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Palladium and iodine approaches to 1,3-dienes, heterocycles and carbocycles

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Palladium and iodine approaches to 1,3-dienes, heterocycles and carbocycles

by

Xiaoxia Zhang

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock, Major Professor
Klaus Schmidt-Rohr
Walter Trahanovsky
Robert Angelici
William Jenks

Iowa State University

Ames, Iowa

2005

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Major Professor

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For the Major Program

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LIST OF ABBREVIATIONS

aq	aqueous
Bu	butyl
t-Bu	*tert*-butyl
cat.	catalytic
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyanoquinone
DMF	*N*,*N*-dimethylformamide
dt	doublet of triplets
eq	equation
equiv	equivalent
Et	ethyl
h	hour
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
m	multiplet
Me	methyl
mL	milliliter
mol	mole
mp	melting point

MS	mass spectrometry
n	normal
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
q	quartet
s	singlet
t	triplet
satd	saturated
t	triplet
TBAC	tetra-*n*-butylammonium chloride
tert	tertiary
TLC	thin layer chromatography
TMS	trimethylsilyl
tt	triplet of triplets
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl

ABSTRACT

A variety of highly-substituted 1,3-dienes and 1,3,5-trienes have been regio- and stereoselectively prepared by the palladium-catalyzed coupling of vinylic iodides, internal alkynes and organoboranes in moderate to good yields. The analogous three-component coupling of aryl halides, 1,3-dienes, and boronic acids provides a useful route to 3,6-disubstituted cyclohexenes. This method is a very concise and efficient way to synthesize these molecules, whose synthesis has previously required multi-step synthesis.

A wide variety of substituted quinolines have been readily synthesized under mild reaction conditions by the 6-*endo*-dig electrophilic cyclization of *N*-(2-alkynyl)anilines by ICl, I_2, Br_2 and PhSeBr. The reaction affords 3-halogen-, selenium- and sulfur-containing, and 4-aryl-, alkyl- and vinylic quinolines in moderate to good yields. Quinolines bearing a hydrogen in the 3-position have been synthesized by the $Hg(OTf)_2$-catalyzed ring closure of these same alkynylanilines.

Substituted naphthalenes are readily prepared regioselectively under mild reaction conditions by the 6-*endo*-dig electrophilic cyclization of appropriate arene-containing propargylic alcohols with ICl, I_2, Br_2, NBS and PhSeBr. 3-Iodo-2-naphthols have also been prepared in excellent yields by the cyclization of analogous 1-aryl-3-alkyn-2-ones. This methodology has been successfully extended to the synthesis of substituted carbazoles and dibenzothiophenes and readily accommodates various functional groups.

The electrophile-induced intramolecular *ipso*-cyclization of 4-methoxyaryl alkynes provides an efficient approach to various 3-halogen-substituted spirotrienones under very mild reaction conditions. Substituted spiro[4.5]trienones, 1-azaspiro[4.5]trienones,

spiro[4.5]diones, 1-oxaspiro[4.5]diones, and 1-azaspiro[4.5]diones are all readily synthesized. ICl, I_2 and Br_2 are all effective electrophiles for this process.

Arynes generated *in situ* from 2-(trimethylsilyl)aryl triflates and CsF undergo annulation by *o*-haloarenecarboxaldehydes in the presence of a Pd catalyst, providing a useful new method for the synthesis of fluoren-9-ones in good yields.

GENERAL INTRODUCTION

Palladium-catalyzed reactions are extremely useful synthetic methods for carbon-carbon and carbon-heteroatom bond formation due to their ability to tolerate a wide range of important organic functional groups, their relative stability to moisture and air, and the possibility of fine tuning their reactivity by the proper choice of the ligands, bases and other additives.

1,3-Dienes and 1,3,5-trienes are important products or intermediates in organic chemistry. They are of great interest for their photochemical, electrochemical, and biological properties. Multi-component reactions have attracted much attention from chemists, because they are highly efficient, economical, and can achieve high molecular complexity in a single step. In Chapter 1 of this thesis, we have successfully developed efficient methodology for the synthesis of dienes and trienes through a Pd-catalyzed ternary cross-coupling reaction.

The Larock group has shown previously that the palladium-catalyzed annulation of alkynes by functionally-substituted aryl halides is a very efficient method for the construction of a wide variety of heterocycles and carbocycles. In this dissertation, similar, but unprecedented carbopalladation reactions of arynes by 2-iodobenzaldehydes are realized providing a useful synthesis of fluoren-9-one and derivatives.

All of the above reactions start from various substituted aryl halides, especially aryl iodides and bromides. Thus, development of simple and efficient methods to the synthesis of aryl halides is highly desirable.

In a recent series of papers, the electrophilic cyclization of functionally-substituted alkynes has been shown to be a very promising route to an extraordinary range of medicinally-interesting, functionally-substituted heterocycles and carbocycles substituted by

halogen atoms. The highlights of this attractive and efficient approach include: (1) the mild reaction conditions and tolerance of considerable functionality; (2) the use of readily available starting materials; and (3) facile elaboration of the iodine functionality to construct more complex molecules. We have discovered that substituted quinolines, naphthalenes, naphthols, and a number of structurally interesting spiro[4.5]trienones can be readily synthesized using this basic electrophilic cyclization chemistry.

Dissertation Organization

This dissertation is divided into five chapters. Each of these chapters is written up following the guidelines for a full paper in the *Journal of Organic Chemistry*.

Chapter 1 investigates the synthesis of 1,3-dienes and 1,3,5-trienes by the Pd-catalyzed coupling reaction of vinylic halides, internal alkynes, and organoboranes. "Optimal" reaction conditions have been discovered and a wide variety of dienes and trienes have been synthesized in reasonable to excellent yields using these conditions.

Chapter 2 reports the synthesis of substituted quinolines by the electrophilic cyclization of *N*-(2-alkynyl)anilines and *N*-(2-alkynyl)triflamides. The scope of this methodology and its application in palladium-catalyzed coupling reactions are examined in detail.

Chapter 3 expands this electrophilic cyclization chemistry to the synthesis of naphthalenes, 2-naphthols, carbazoles and dibenzothiophenes. Arene-containing propargylic alcohols, methyl ethers, propargylic esters, and 1-aryl-3-alkyn-2-ones are all versatile starting materials for this process.

Chapter 4 presents the synthesis of a variety of spiro[4.5]trienones. Different reaction conditions have been developed for different systems. *Ipso* and *ortho* cyclization can be turned "on" and "off" at will when appropriate reaction conditions are employed.

Chapter 5 describes a novel palladium-catalyzed annulation of a variety of arynes to synthesize fluoren-9-ones. This process involves arylpalladation of the aryne, followed by intramolecular coupling with the formyl group.

Finally, all of the ^{1}H and ^{13}C NMR spectra for the starting materials and reaction products have been compiled in appendices A-E following the general conclusions for this dissertation.

Chapter 1. Synthesis of Highly Substituted 1,3-Dienes and 1,3,5-Trienes by the Palladium-Catalyzed Coupling of Organic Halides, Internal Alkynes, and Organoboranes

Based on a paper to be submitted to the *Journal of Organic Chemistry*

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Abstract

A number of highly substituted 1,3-dienes and 1,3,5-trienes have been stereoselectively prepared in moderate to good yields by the coupling of vinylic iodides, internal alkynes, and organoboranes in the presence of a palladium catalyst. Optimal reaction conditions for different organoboron substrates have been developed. The analogous three-component coupling of aryl halides, 1,3-cyclohexadiene, and boronic acids provides a synthetically useful route to 3,6-disubstituted cyclohexenes. These methods are very efficient and provide a concise way to synthesize the indicated alkenes, dienes and trienes, whose preparation would normally require multi-step synthesis.

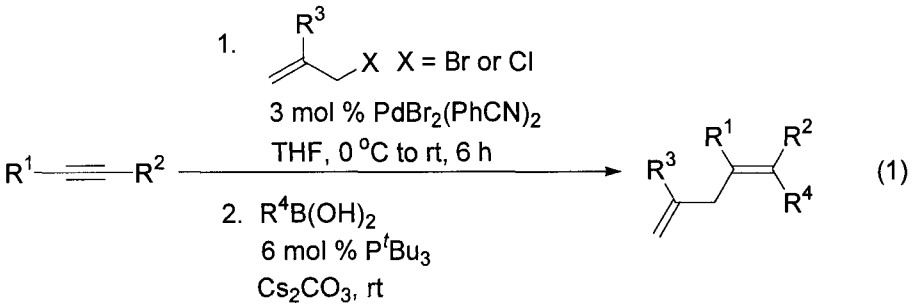
Introduction

1,3-Dienes and 1,3,5-trienes are important products or intermediates in organic chemistry.[1] They are of great interest for their photochemical, electrochemical, and biological properties.[2] While there are numerous previous methods to prepare simple dienes and trienes, the regio- and stereoselective construction of highly-substituted dienes and

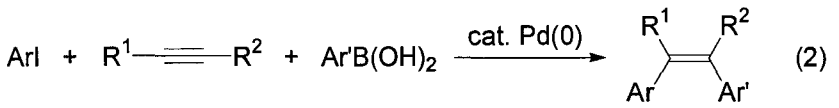
trienes, and especially those bearing tetrasubstituted double bonds, remains one of the biggest challenges in organic synthesis.[3] Therefore, a strategic and diverse approach to such olefins is highly desirable.

The propensity of unsaturated compounds, such as alkenes, allenes, 1,3-dienes and alkynes, to undergo insertion into carbon-metal bonds makes these substrates some of the most useful for transition metal-catalyzed organic transformations.[4] Organoboronic acids and borates are widely used in the palladium-catalyzed Suzuki coupling with organic halides, providing an extremely useful route for carbon-carbon bond formation.[5] Thus, the palladium-catalyzed sequential ternary coupling of organic halides, unsaturated compounds and organoboronic acids is expect to be a highly efficient process employing multiple reaction steps in a single pot. The practical advantage of the Suzuki reaction compared with other coupling reactions lies in the fact that boronic acids are readily prepared, nontoxic and thermally, air, and moisture stable, as well as being compatible with diverse functional groups.

Rawal et al. have reported the synthesis of skipped dienes by the palladium-catalyzed allylation of alkynes and a subsequent Suzuki cross-coupling reaction (eq 1).[6] Grigg and co-workers have synthesized polycyclic compounds bearing a substituted 1,3-diene moiety through the *intramolecular* tandem reaction of an aromatic halide with an internal alkyne, followed by cross-coupling with an external vinylic catecholborane.[7]

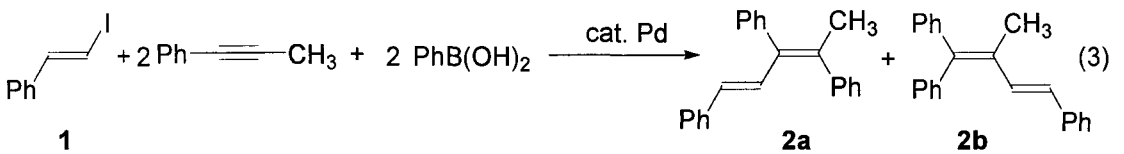


We have previously reported[8] a highly efficient, stereo- and regioselective synthesis of tetrasubstituted olefins by the palladium-catalyzed cross-coupling of aryl halides, internal alkynes and arylboronic acids (eq 2). Herein, we report full details of our investigation of a one-pot, *intermolecular* palladium-catalyzed coupling of vinylic halides, internal alkynes, and aryl or vinylic boron organometallics, which offers an efficient, direct route for the construction of a number of highly substituted 1,3-dienes or 1,3,5-trienes in a chemo-, regio-, and stereoselective manner from simple, readily available starting materials.[9]



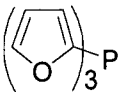
Results and Discussion

Optimization. Our initial work was aimed at developing a set of palladium conditions that would work well for a variety of substrates. The reaction of vinylic iodide **1**, 1-phenylpropyne, and phenylboronic acid was chosen as the model system for optimization of this process (eq 3), and the results are summarized in Table 1.



The original set of reaction conditions used included 5 mol % $PdCl_2(PhCN)_2$, 1 equiv of K_2CO_3 and 10 mL of 5:1 DMF/H_2O as the solvent at 100 °C in the presence of air, conditions which were developed[8] for our previous three-component coupling reaction of aryl halides, internal alkynes and arylboronic acids (entry 1, Table 1). Here, we have chosen the vinylic iodide as the limiting reagent simply because it is generally less readily available and usually must be prepared in the lab, while many alkynes and boronic acids are commercially available.

Table 1. Optimization of the Reaction of Vinylic Iodide 1, 1-Phenylpropyne, and Phenylboronic acid[a]

entry	base (equiv)	Pd catalyst	temp. (°C)	DMF/H_2O	% yield of **2**
1	K_2CO_3 (1)	$PdCl_2(PhCN)_2$	100	5:1	45
2	K_2CO_3 (1)	$PdCl_2$	100	5:1	46
3	K_3PO_4 (1)	$PdCl_2$	100	5:1	38
4	KF (2)	$PdCl_2$	100	5:1	51[b]
5	KF (2)	$PdCl_2(PPh_3)_2$	100	5:1	25
6	KF (2)	$PdCl_2$, 	100	5:1	16
7	KF (2)	$Pd_2(dba)_3$	100	5:1	45
8	KF (2)	$PdCl_2$	80	5:1	40
9	KF (2)	$PdCl_2$	RT[c]	5:1	29
10	KF (2)	$PdCl_2$	100	7:1	37
11	KF (2)	$PdCl_2$	100	100:0	32
12	KF (2)	$PdCl_2$	100	5:2	23

[a] All reactions were run using 0.25 mmol of iodide **1**, 0.5 mmol of alkyne, and 0.5 mmol of phenylboronic acid, employing 5 mol % of the Pd catalyst, plus 10 mol % of a phosphine in 10 mL of DMF/H_2O for 2 h unless otherwise specified. [b] The two regioisomers were obtained in a 40:60 (**2a**:**2b**) ratio. [c] The reaction was incomplete after 24 h, and the two regioisomers were obtained in a 37:63 (**2a**:**2b**) ratio.

Using $PdCl_2$ as a catalyst gave a yield comparable to that of $PdCl_2(PhCN)_2$ (Table 1, compare entries 1 and 2). Using $PdCl_2$ as the palladium source and K_3PO_4 as a base resulted in a lower yield (entry 3). However, the use of KF as the base improved the yield (entry 4). The weak basicity and poor nucleophilicity of the fluoride ion could make this base particularly useful in the case of base-sensitive substrates. Adding triphenylphosphine or tri-2-furylphosphine as ligands slowed down the reaction and lowered the yield (entries 5 and 6). Using a Pd(0) catalyst, $Pd_2(dba)_3$, provided the same yield as that of $PdCl_2$ (entry 7). Contrary to our previous observations that much better regioselectivities for the coupling of aryl iodides, internal alkynes and boronic acids could be achieved at room temperature,[8] a higher reaction temperature here not only shortened the reaction time, it gave a better yield than the room temperature reaction, although the effect of the reaction temperature on the regioselectivity of the reaction is minimal (compare entries 4 and 9). We, therefore, chose 100 °C as the optimal reaction temperature. The presence of water greatly facilitates the desired reaction (entries 10 and 11), perhaps because water is needed to dissolve the KF base, and F^- or OH^- ion combines with the arylboronic acid to form an "ate complex", which is crucial in Suzuki cross-coupling reactions.[5,10] With insufficient water, substantial amounts of fulvenes are formed by the double insertion of alkynes, followed by ring closure, without the involvement of the boronic acid.[11] However, too much water helps the direct Suzuki reaction of the vinylic iodide and the arylboronic acid and is detrimental to the yield of the desired sequential three-component coupling (entry 12). We thus settled on the following "optimal" conditions A employing 1 equiv of vinylic halide, 2 equiv of internal alkyne, 2 equiv of arylboronic acid, 5 mol % of $PdCl_2$, 2 equiv of KF, and 5:1 DMF/H_2O as the solvent at 100 °C in the presence of air. This "optimal" procedure has thus been employed on a variety of

representative substrates, which were carefully selected in order to establish the generality of the process and its applicability to commonly encountered synthetic problems. While the yields from this model system are not particularly high, subsequent research established that our "optimal" procedure actually works quite well when a number of different vinylic halides, alkynes and boronic acids are employed (Table 2).

Table 2. Palladium-Catalyzed Three-Component Coupling of Vinylic (Aryl) Halides, Internal Alkynes or Cyclohexadienes, and Organoboranes

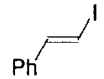
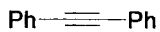
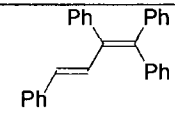
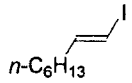
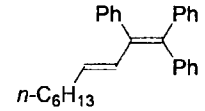
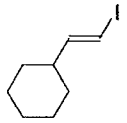
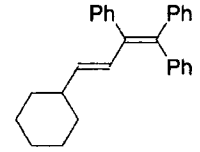
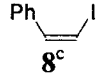
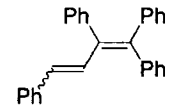
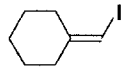
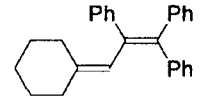
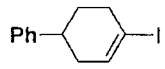
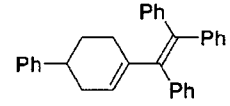
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
1	 **1**		$PhB(OH)_2$	A, 2	 **3**	45
2	 **4**			A, 2	 **5**	62
3	 **6**			A, 2	 **7**	54
4	 **8**[c]			A, 2	 **3**	42[d]
5	 **9**			A, 2	 **10**	87
6	 **11**			A, 2	 **12**	78

Table 2. Continued

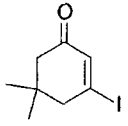
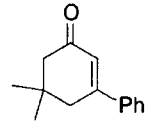
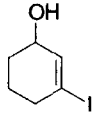
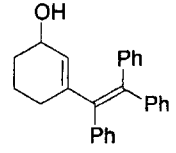
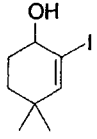
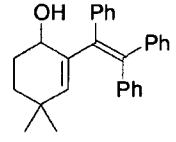
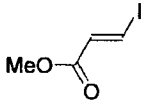
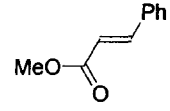
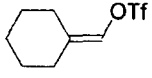
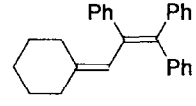
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
7	 **13**			A, 2	 **14**	90
8	 **15**			A, 2	 **16**	41
9	 **17**			A, 2	 **18**	24
10	 **19**			A, 2	 **20**	31
11	 **21**			A, 2	 **10**	30

Table 2. Continued

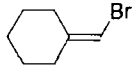
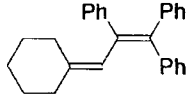
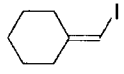
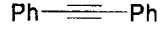
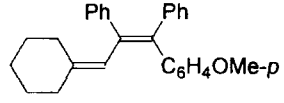
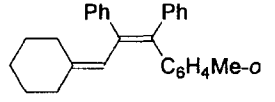
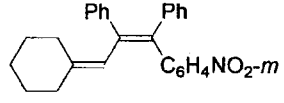
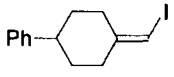
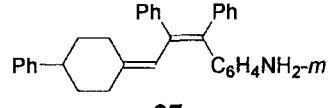
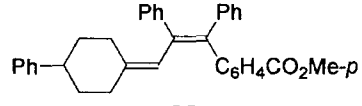
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
12	 **22**			A, 16	 **10**	5
13	 **9**		*p*-$MeOC_6H_4B(OH)_2$	A, 2	 **23**	93
14			*o*-$MeC_6H_4B(OH)_2$	A, 2	 **24**	82
15			*m*-$O_2NC_6H_4B(OH)_2$	A, 2	 **25**	56
16	 **26**		*m*-$H_2NC_6H_4B(OH)_2$	A, 2	 **27**	86
17			*p*-$MeO_2CC_6H_4B(OH)_2$	A, 2	 **28**	60

Table 2. Continued

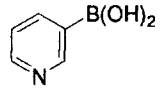
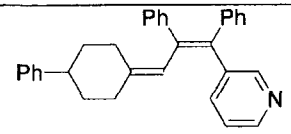
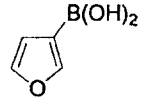
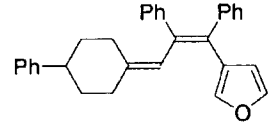
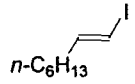
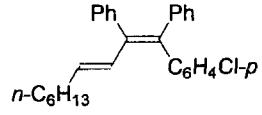
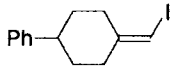
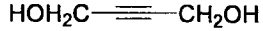
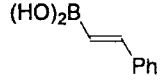
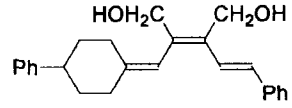
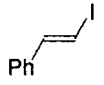
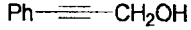
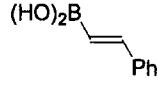
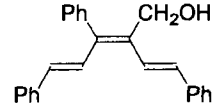
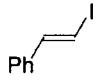
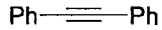
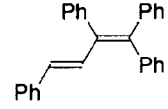
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
18				A, 2	 **29**	63
19				A, 2	 **30**	68
20	 **4**		p-$ClC_6H_4B(OH)_2$	A, 2	 **31**	37
21	 **26**			A, 2	 **32**	31, 57[c]
22	 **1**			A, 2	 **33**	32
23	 **1**		$NaBPh_4$	B, 12	 **3**	71

Table 2. Continued

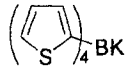
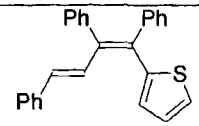
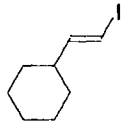
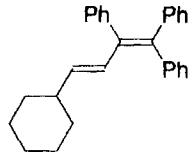
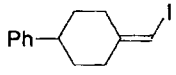
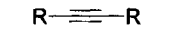
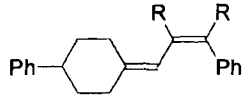
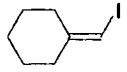
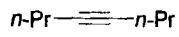
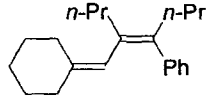
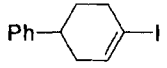
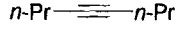
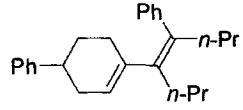
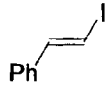
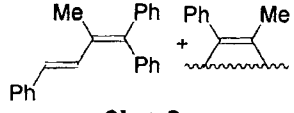
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
24				B, 12	 **34**	80
25	 **6**		KBF_3Ph	A, 12	 **7**	31[f]
26	 **26**	 $R = C_6H_4CO_2Et\text{-}p$	$PhB(OH)_2$	A, 2	 **35**	68
27	 **9**			A, 2	 **36**	85
28	 **11**			A, 2	 **37**	63
29	 **1**			A, 2	 **2b + 2a**	51[g] (60:40)

Table 2. Continued

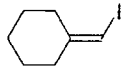
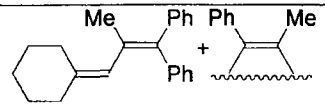
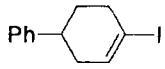
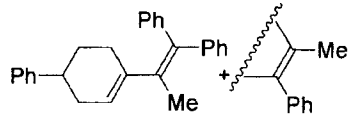
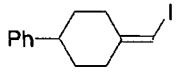
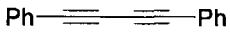
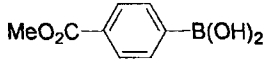
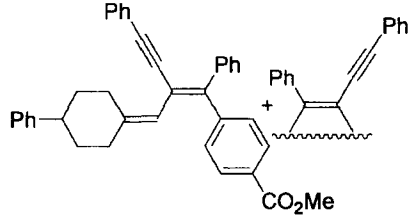
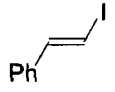
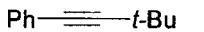
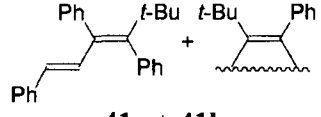
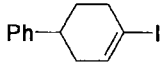
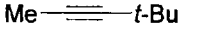
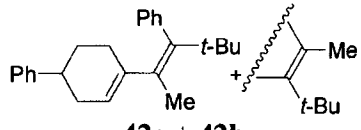
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
30	 **9**			A, 2	 **38a** + **38b**	90[g] (59:41)
31	 **11**			A, 2	 **39a** + **39b**	71[g] (56:44)
32	 **26**			A, 2	 **40a** + **40b**	62[g] (88:12)
33	 **1**		$PhB(OH)_2$	A, 2	 **41a** + **41b**	60[g, h] (85:15)
34	 **11**		$PhB(OH)_2$	A, 2	 **42a** + **42b**	35[g] (95:5)

Table 2. Continued

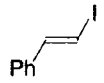
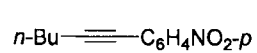
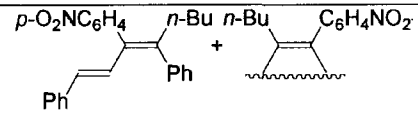
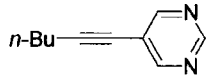
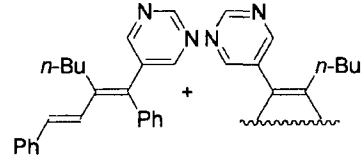
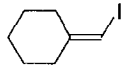
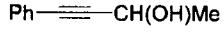
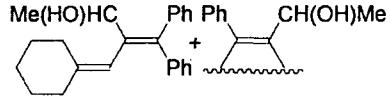
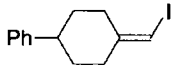
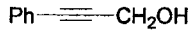
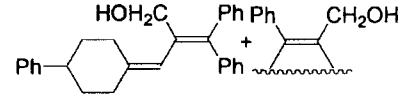
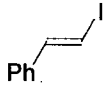
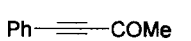
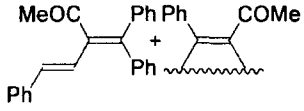
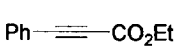
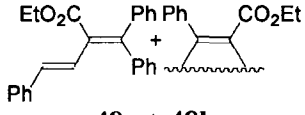
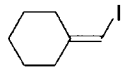
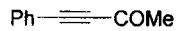
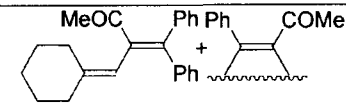
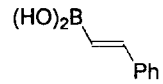
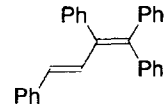
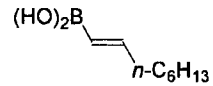
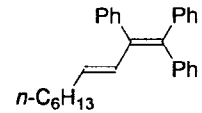
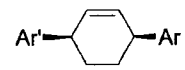
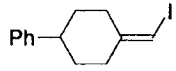
entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield[b]
35	 **1**			A, 2	 **43a** + **43b**	62[g] (86:14)
36				A, 2	 **44a** + **44b**	60[g] (83:17)
37	 **9**			A, 2	 **45a** + **45b**	93[g] (70:30)
38	 **26**			A, 4	 **46a** + **46b**	85[g] (68:32)
39	 **1**			A, 2	 **47a** + **47b**	71[g] (63:37)
40				A, 2	 **48a** + **48b**	62[g] (68:32)

Table 2. Continued

entry	halide	alkyne or cyclohexadiene	organoborane	cond.,[a] time (h)	product(s)	% yield [b]
41	 **9**			A, 2	 **49a + 49b**	82[g] (71:29)
42	PhI			C, 4	 **3**	58
43				C, 4	 **5**	51
44	*p*-MeC_6H_4I		$PhB(OH)_2$	D, 24	 **50**	59[i]
45	*p*-$H_2NC_6H_4I$			D, 24	**51**	89
46	*p*-HOC_6H_4I			D, 24	**52**	70
47	*p*-$MeOC_6H_4I$			D, 24	**53**	58
48	*p*-$MeCOC_6H_4I$			D, 24	**54**	0
49	*o*-MeC_6H_4I			D, 24	**55**	19
50	*p*-$H_2NC_6H_4I$		*o*-$MeC_6H_4B(OH)_2$	D, 24	**56**	72
51	*p*-$H_2NC_6H_4I$		*p*-$ClC_6H_4B(OH)_2$	D, 24	**57**	53
52	 **26**		$PhB(OH)_2$	D, 24	**58**	88

[a] See the text for Conditions A-D. [b] Isolated yield. [c] This compound was prepared and utilized as an 86:14 mixture of *Z*/*E* isomers. [d] The product was obtained as a 2.5:1 mixture of *E*- and *Z*-stereoisomers. [e] 6 Equiv of KF was employed. [f] Only trace amount of **7** was obtained without KF as base. [g] The products are inseparable. [h] The reaction was run employing a ratio of iodide:alkyne:boronic acid = 2:1:2. [i] The yield was determined by ^{1}H and ^{13}C NMR analysis.

Scope of the Vinylic Halide. The scope and limitations of this reaction for the synthesis of a wide variety of 1,3-dienes are indicated in Table 2. Moderate yields of the desired 1,3-dienes were obtained from the reaction of *β*-monosubstituted *trans*-vinylic iodides (entries 1-3, Table 2) with diphenylacetylene and phenylboronic acid. In all of these reactions, we were able to separate 20-30% of the product from direct coupling of the vinylic iodides and phenylboronic acid, together with small amounts of tetraphenylethene, which is apparently formed by the reaction of phenylboronic acid and phenylacetylene.[11] In all cases, geometrically pure dienes were obtained when using (*E*)-alkenes as determined by GC-MS and ^{1}H and ^{13}C NMR spectroscopy. When an 86:14 mixture of *Z*- and *E*-*β*-iodostyrene was employed, a 2.5:1 mixture of the corresponding *E*- and *Z*-stereoisomeric 1,3-dienes was obtained, indicating substantial loss of stereochemistry during this particular coupling process. The thermodynamically more stable and configurationally inverted *E*-isomer **3** was generated as the major isomer (entry 4). The desired reaction proceeded very efficiently when the *β*,*β*-disubstituted vinylic iodide **9** and 1-iodo-4-phenylcyclohexene (**11**) were employed (entries 5 and 6). However, the reaction of 3-iodo-5,5-dimethylcyclohex-2-enone (**13**) and diphenylacetylene afforded a product in which the vinylic halide and arylboronic acid had undergone direct cross-coupling without insertion of the alkyne (entry 7). None of the desired 1,3-diene was observed. Obviously, an electron-withdrawing group on the *β*-position of the vinylic halide greatly facilitates direct nucleophilic transmetalation of the boronic acid by the organopalladium(II) intermediate, rather than alkyne insertion, resulting in the monoene product (see the later mechanistic discussion). On the other hand, the hydroxy-containing vinylic halide **15** reacts with diphenylacetylene under our standard reaction conditions to give the desired dienol **16** in a 41% yield, which should be easily

oxidized to the corresponding ketone. Placing the halide nearer the alcohol functionality resulted in a still lower 24% yield of the desired diene **18**, alongside a 59% yield of the direct Suzuki product 4,4-dimethyl-2-phenylcyclohex-2-en-1-ol (entry 9). The presence of a vicinal OH group is apparently detrimental to carbopalladiation of the alkyne. The reaction of methyl *trans*-2-iodoacrylate generated a 31% yield of methyl cinnamate without any of the desired diene being detected. It appears that this iodide is unstable under our reaction conditions. A vinylic triflate has been cross-coupled using this process, although a much lower yield was observed than that obtained using the analogous iodide (compare entries 5 and 11). Unfortunately, the analogous vinylic bromide proved to be essentially inert in this process (entry 12). Only a 5% yield of the expected diene was formed after 16 h reaction and most of the vinylic bromide remained unreacted.

Scope of the Boronic Acid. A wide variety of dienes can be synthesized in excellent yields from the reaction of vinylic iodide **9**, diphenylacetylene, and various functionally-substituted arylboronic acids. For example, the electron-rich arylboronic acid *p*-methoxyphenylboronic acid (entry 13) and the relatively hindered *o*-tolylboronic acid (entry 14) gave excellent yields of dienes. However, the yield dropped considerably when a relative electron-poor boronic acid, like 3-nitrophenylboronic acid, was employed (entry 15). The generation of substantial amounts of the direct cross-coupling product 3-nitrobenzylidenecyclohexane accounts for the decrease in the yield. Similar electronic effects have been observed in the reactions of vinylic iodide **26** and 3-aminophenylboronic acid (entry 16) and 4-ethoxycarbonylphenylboronic acid (entry 17). While the former boronic acid gave an 86% yield of product, the yield dropped to 60% for the latter boronic acid. Using *E*-1-iodo-1-octene and 4-chlorophenylboronic acid, instead of phenylboronic

acid, resulted in the yield dropping from 62% to 37% (compare entry 2 with entry 20). We were pleased to find that important heterocyclic moieties, such as furyl and pyridyl groups, can be successfully incorporated into dienes using our procedure and the corresponding boronic acids (entries 18 and 19).

The nature of the boronic acid was expanded to alkenyl variants to generate 1,3,5-trienes. When vinylic iodide **26** was allowed to react with 2-butyne-1,4-diol and styrylboronic acid under the standard reaction conditons, triene **33** was generated in a 31% yield. The yield could be further improved to 57% when 6 equiv of KF were employed, but further increasing the equivalents of KF to 10 lowered the yield to 48% (entry 21). The synthesis of trienes utilizing β-iodostyrene has consistently given lower yields than other more substituted vinylic iodides (entry 22).

Unfortunately, extensive optimization efforts devoted towards incorporating alkyl, allyl, and cyclopropyl groups from the corresponding boronic acids or esters have proven fruitless when employing vinylic iodide **1** and diphenylacetylene. Under conditions A, all of the above boronic acids afforded products of vinylpalladium addition to the alkyne, followed by hydrogen substitution of the Pd moiety. It is unclear where the hydrogen is coming from. We hypothesize that it might be coming from formate possibly produced by the hydrolysis of the DMF in the presence of base.[13]

Other organometallics can also be employed in these cross-coupling reactions. For example, when $PhB(OH)_2$ was replaced by $NaBPh_4$, the desired diene was obtained under non-aqueous and non-basic conditions. The "optimal" reaction conditions B for this process utilize 2 equiv of the vinylic halide, 1 equiv of the internal alkyne, 2 equiv of borate, 5 mol % of $Pd(OAc)_2$, and 1 equiv of LiCl in DMF at 100 °C in the presence of air.[13] Under these

conditions, vinylic halide **1** reacts with diphenylacetylene and $NaBPh_4$ to afford the desired product **3** in a 71% yield (entry 23). Transmetallation of a thiophene group from sodium tetra(2-thiophenyl)borate was even more facile, producing **34** in an 80% yield (entry 24). The reaction of potassium phenyltrifluoroborate also provides the desired 1,3-diene **7** in a lower yield (compare entry 3 and 25). It is noteworthy that the base is still necessary in the reaction, since only a trace amount of the product is obtained without the KF base.

Scope of the Internal Alkyne. Under our "optimal" conditions, a wide variety of internal alkynes have been successfully employed in all cases studied so far. The reactions proceeded in a very stereoselective manner. When symmetrical alkynes, such as diphenylacetylene or 4-octyne, are employed, only one pure stereoisomer was generated and the vinylic group and the aryl group from the arylboronic acid has been unambiguously determined by NOSEY experiments (see Supporting Information) to exist in a *cis*-configuration. Diaryl and more electron-rich dialkyl acetylenes have provided the desired 1,3-dienes in excellent yields (entries 26-28), as opposed to the generation of substantial amounts of multi-alkyne insertion products in the analogous coupling of aryl iodides and 4-octyne.[8]

Two isomers have generally been obtained with moderate to excellent regioselectivity when unsymmetrical alkynes are employed. The regiochemistry is primarily controlled by steric effects in all examples so far examined. The initial vinylic palladium intermediate usually adds the Pd moiety to the more hindered end of the triple bond, where the longer carbon-palladium bond is presumably more favorable energetically than the shorter carbon-carbon bond that is formed. Thus, the vinylic group generated from the vinylic halide generally adds to the less hindered end of the alkyne, while the aryl group from the

arylboronic acid adds to the other end of the alkyne. Obviously, the greater the difference in the size of the two groups attached to the end of the alkyne, the better the regioselectivity is expected to be. Moderate selectivity was observed for 1-phenylpropyne, no matter what vinylic halide was employed (entries 29-31). The regioselectivity was improved greatly when using 1,4-diphenylbutadiyne (entry 32). Quite good regioselectivities were obtained for 1-phenyl-3,3-dimethyl-1-butyne (entry 33) and 4,4-dimethyl-2-butyne (entry 34). The relatively low yield from 4,4-dimethyl-2-butyne may in part be due to the fact that 4,4-dimethyl-2-butyne is relatively volatile (bp 80 °C) under our standard reaction conditions (100 °C). These results are consistent with our and others' previous work[13,15] on palladium-catalyzed additions to alkynes.

Electronic effects also play an important role in the regiochemistry. The aryl group from the arylboronic acid prefers to add to the more electron-poor end of the alkyne, assuming steric effects are comparable. Therefore, surprisingly high 86:14 regioselectivity is observed when 1-(4-nitrophenyl)-1-hexyne is used as the alkyne (compare entry 35 with entry 29). In the absence of the nitro group, we get only a 60:40 ratio of regioisomeric dienes in a 44% yield. Substitution of the phenyl group with an electron-poor pyrimidine group has a similar effect (compare entry 36 and 29). When the steric and electronic effects work in opposition to each other, relative poor regioselectivity is expected and indeed observed, as seen in examples involving a ketone- or ester-containing internal alkyne (entries 39-41). In these cases, steric effects apparently overrule electronic effects (presumably the phenyl group is more sterically hindered than the ketone or ester groups, and the ketone and ester groups are more electron-poor than the phenyl group).

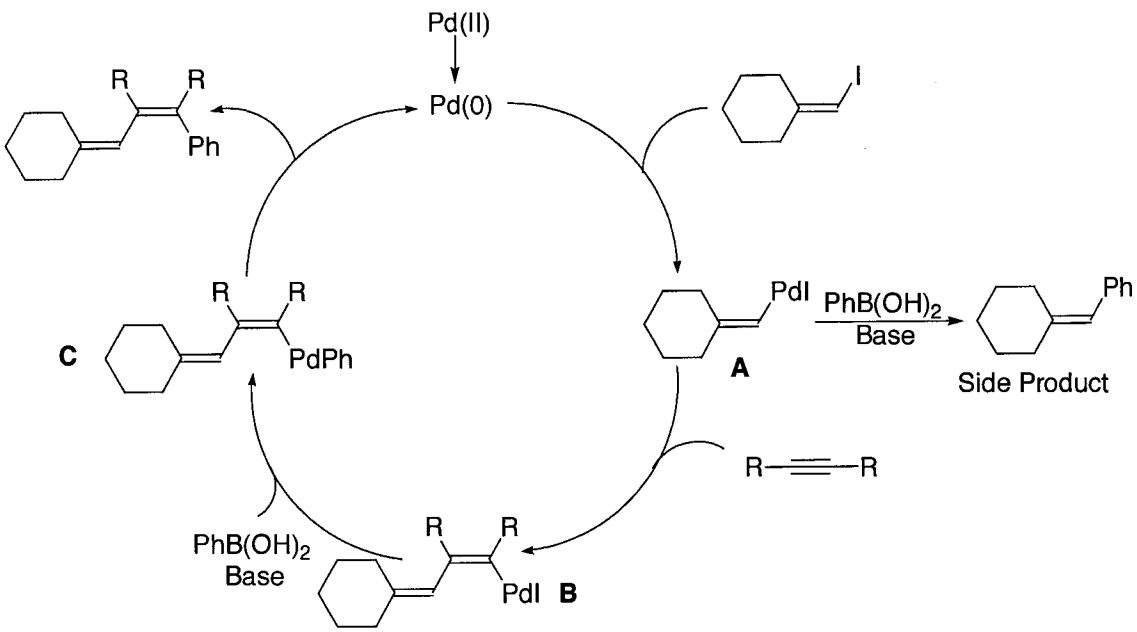
This process is tolerant of considerable functionality. Thus, ketone, ester, nitro, and alcohol (entries 37 and 38) functional groups are readily accommodated, providing the desired tetrasubstituted olefins in good to excellent yields. However, the cross-coupling reactions of these halides with terminal alkynes (either phenylacetylene or 1-heptyne) do not give clean products. The desired product; the product generated by carbopalladation of the alkyne by the vinylic halide, followed by cross-coupling of the vinylic palladium intermediate with the terminal alkyne in a Sonogashira-type reaction; along with side products formed by direct coupling of the vinylic halide and either the boronic acid or the terminal alkyne were all generated, making the reaction fairly messy.

It seemed obvious that the regiochemistry of the 1,3-dienes should be readily reversed if one were to start with an aryl iodide and cross-couple with a vinylic boronic acid. Thus, PhI, diphenylacetylene, and styrylboronic acid was allowed to reacted under conditions A. Unfortunately, only around 5% of the desired product **3** was obtained and *trans*-1,2-diphenylethene was the primary product. We later found that reasonable yields of **3** and **5** can be obtained by employing 5 mol % of $PdCl_2(PhCN)_2$, 1 equiv of the aryl halide (0.25 mmol), 2 equiv of alkyne, 2 equiv of the vinylic boronic acid, 1 equiv of *n*-Bu_4NCl (TBAC), 50 equiv of H_2O and 8 mL of DMF as the solvent at 100 °C in the presence of air for 12 h (entries 41 and 42). Without TBAC, the yield of the reaction discussed in entry 41 dropped to 40%. 50 Equiv of H_2O appears to be optimal, at least for this reaction.

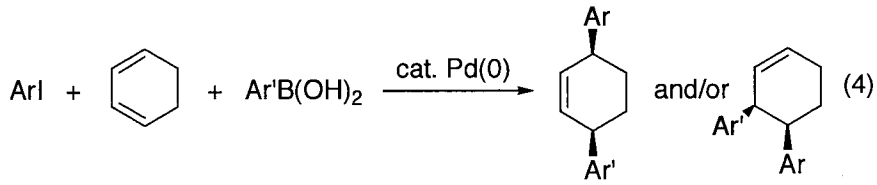
Mechanism. We propose the following mechanism, which involves the following key steps for this three-component coupling reaction (Scheme 1): (1) reduction of Pd(II) to the actual catalyst Pd(0),[16] (2) oxidative addition of the vinylic iodide to Pd(0) to produce a vinylic palladium intermediate **A**, (3) vinylpalladium coordination to the alkyne and

subsequent *cis* insertion to form a new vinylpalladium intermediate **B**, (4) transmetalation with an "ate" complex of the organoborane to form intermediate **C**, and (5) reductive elimination of the product with regeneration of the Pd(0) catalyst. All steps are well precedented in organopalladium chemistry.[17] While the majority of the reactions reported here are quite clean, in reactions affording much lower yields of dienes, side products consistent with this mechanism are observed.

Scheme 1



Cross-coupling of 1,3-Cyclohexadiene. A synthetically interesting question is whether one can achieve the analogous coupling of aryl or vinylic halides with 1,3-dienes, followed by quenching of the resulting π-allylpalladium intermediate with a boronic acid (eq 4). Our success in the reactions of alkynes prompted us to investigate this intriguing reaction.

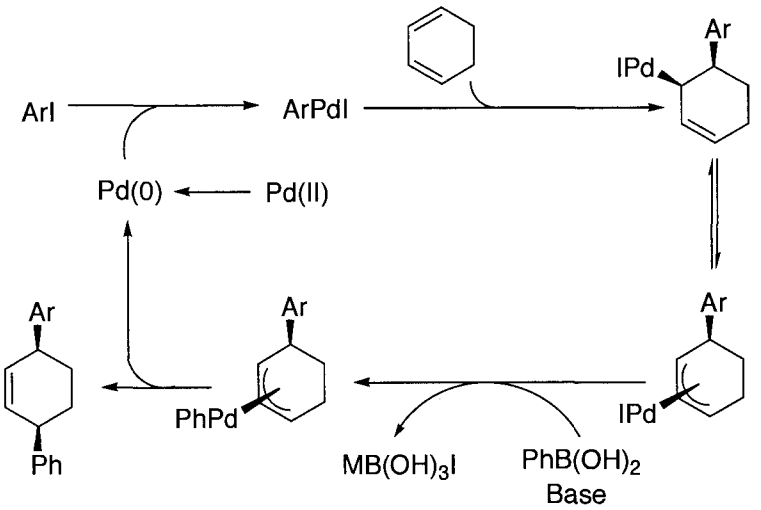


A brief optimization study indicated that a reaction involving 1 equiv of *p*-tolyl iodide, 4 equiv of 1,3-cyclohexadiene, 2 equiv of phenylboronic acid, 5 mol % of $PdCl_2(PhCN)_2$, 2 equiv of KF, and 5:1 DMF/H_2O as the solvent at 100 °C in the presence of air (Conditions D) provided the desired alkene in a 59% yield (entry 44). The yield dropped to 50% when 2 equiv of K_2CO_3 were used as the base. The reaction became sluggish when water wasn't employed as the co-solvent. Based on known palladium chemistry, both 3,6-diarylcyclohexene and 3,4-diarylcyclohexene are possible products.[17a] However, only one isomer was detected in our study through GC-MS and ^1H and ^{13}C NMR experiments. The major product is believed to be the thermodynamically more stable *cis*-3,6-diarylcyclohexene as indicated by ^1H and ^{13}C NMR spectral analysis. An interesting feature of this chemistry is that reactions employing electron-rich aryl iodides, such as 4-iodoaniline (entry 45), 4-iodophenol (entry 46) or 4-iodoanisole (entry 47) give the best yields and more importantly, free NH_2 and OH groups, which are known to be reactive nucleophiles in reactions with π-allylpalladium intermediates[18] remain untouched under our reaction conditions (entries 45-47). The higher yields obtained with these substrates presumably arise because the electron-releasing groups decrease the electrophilicity of the arylpalladium intermediate and thus suppress direct coupling with the boronic acid. In fact, when 4-iodoacetopheone was allowed to react with 1,3-cyclohexadiene and phenylboronic acid, none of the desired alkene product was observed (entry 48). Instead, 4-acetylbiphenyl was formed primarily. Unfortunately, the presence of a group in the *ortho*-position of the aryl iodide appears to be a

problem also, since the yield dropped significantly (entry 49). On the other hand, the presence of a methyl group *ortho* to the boronic acid only slightly lowered the yield (entry 50). The yield also dropped when 4-chlorophenylboronic acid was employed (entry 51). We were pleased to find that a vinylic iodide **26** can be successfully employed in this process to generate a 1,4-skipped diene (entry 52). Unfortunately, other dienes, such as 1,3-cycloheptadiene and 2-methyl-1,3-butadiene failed to generate synthetically useful yields of the desired products. Direct cross-coupling of the aryl halide and arylboronic acid was the dominant process in the former reaction, while in the later case, the major product was the Heck product produced by β-hydride elimination of the π-allylpalladium intermediate as determined by GC-MS.

We believe that a mechanism similar to that of Scheme 1 is involved here (Scheme 2). The key steps are: (1) reduction of Pd(II) to the actual catalyst Pd(0),[16] (2) oxidative addition of the aryl iodide to Pd(0) to produce an arylpalladium intermediate, (3) arylpalladium coordination to the 1,3-diene and subsequent *cis* insertion to form a π-allylpalladium intermediate, (4) transmetalation with an "ate" complex of the organoborane to form a new π-allylpalladium intermediate, and (5) reductive elimination of the product with regeneration of the Pd(0) catalyst. All of these steps are well precedented in the organopalladium literature,[17] although it is a bit surprising that reductive elimination of the olefin product is so regioselective. Presumably steric effects strongly favor the less hindered 1,4-addition product.

Scheme 2



Conclusions

In summary, the palladium-catalyzed three-component coupling of vinylic halides, internal alkynes and boron organometallics has been successfully achieved. The reaction is quite efficient, since it allows the selective construction of two carbon-carbon bonds in a single reaction from three simple starting materials. The reaction is insensitive to air and water. A wide range of vinylic halides, organoboron compounds, and internal alkynes with various functional groups can be employed in this process. The reaction involves *cis*-addition to the internal alkyne. The vinylic group from the vinylic iodide favors the less hindered or more electron-rich end of the alkyne, while the aryl group from the arylboronic acid adds to the other end. This generality, combined with the good regio- and stereoselectivity, make this one-pot, two carbon-carbon bond forming process an attractive synthetic route to 1,3-dienes and 1,3,5-trienes bearing a tetrasubstituted carbon-carbon double bond. Finally, the analogous coupling of aryl or vinylic halides with 1,3-

cyclohexadiene, followed by trapping of the π-allylpalladium intermediate with an arylboronic acid has also been successful, providing a stereoselective method to prepare *cis*-3,6-disubstituted cyclohexadienes.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted. (*E*)-β-Iodostyrene, iodomethylenecyclohexane, 1-iodo-4-phenylcyclohexene, bis[4-(ethoxycarbonyl)phenyl]acetylene, 3-iodocyclohex-2-en-1-ol, 3-iodo-5,5-dimethylcyclohex-2-enone and compounds **3**, **10**, **12**, **14**, **16**, **23-25**, **32**, **34-37** and **43** have been previously reported.[9] (*E*)-1-Iodooct-1-ene,[19] (*E*)-2-cyclohexylvinyl iodide,[19] (*Z*)-β-iodostyrene,[20] 2-iodo-4,4-dimethyl-2-cyclohexen-1-ol,[21] cyclohexylidenemethyl triflate[22] and (bromomethylene)cyclohexane[23] were prepared according to previous literature procedures.

Conditions A: To a solution of vinylic halide (0.25 mmol), internal alkyne (0.50 mmol), and $PdCl_2$ (0.0125 mmol) in 5 mL of DMF was added 5 ml of a 2:1 DMF-H_2O solution of KF (0.50 mmol) and the boronic acid (0.50 mmol). The resulting mixture was stirred at room temperature for 3 min in the presence of air, then sealed and heated to 100 °C with stirring for the specified time. **Conditions B**: A mixture of DMF (1.0 mL), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), LiCl (10.5 mg, 0.25 mmol), vinylic halide (0.50 mmol), internal alkyne (0.25 mmol), and tetraarylborate (0.50 mmol) was stirred in a reaction vial at room

temperature for 3 min in the presence of air and then the vial was capped and heated to 100 °C with stirring for the specified time. **Conditions C**: To a solution of vinylic halide (0.25 mmol), internal alkyne (0.50 mmol), water (12.50 mmol), *n*-Bu_4NCl (0.25 mmol), and $PdCl_2(PhCN)_2$ (0.0125 mmol) in 8 mL of DMF was added KF (0.50 mmol) and the boronic acid (0.50 mmol). The resulting mixture was stirred at room temperature for 3 min in the presence of air, then sealed and heated to 100 °C with stirring for the specified time. **Conditions D**: To a solution of aryl halide (0.25 mmol), 1,3-cyclohexadiene (1.00 mmol) and $PdCl_2(PhCN)_2$ (0.0125 mmol) in 10 mL of DMF/H_2O (5:1) was added KF (0.50 mmol) and the boronic acid (0.50 mmol). The resulting mixture was stirred at room temperature for 3 min in the presence of air, then sealed and heated to 100 °C with stirring for the specified time. All reactions were monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (30 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (2 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column. The following 1,3-dienes and 1,3,5-trienes have been prepared using this general procedure.

(*E*)-1,1,2-Triphenyl-1,3-decadiene (5). The reaction mixture was chromatographed using hexanes to afford 57 mg (62%) of the indicated compound as a oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88-0.93 (m, 3H), 1.24-1.32 (m, 8H), 2.02-2.08 (m, 2H), 5.39-5.49 (m, 1H), 6.43-6.48 (d, J = 15.6 Hz, 1H), 6.88-6.91 (m, 2H), 7.01-7.05 (m, 3H), 7.14-7.21 (m, 5H), 7.29-7.38 (m, 5H), 6.55-6.57 (m, 2H), 6.70-6.72 (d, J = 7.6 Hz, 1H), 6.95-6.98 (m, 2H), 7.04-7.45 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.18, 22.71, 28.93, 29.27, 31.75, 33.22,

125.94, 126.40, 126.97, 127.33, 127.71, 127.94, 131.10, 131.12, 131.49, 132.25, 136.21, 139.04, 139.76, 141.12, 142.81, 143.20; IR (CH_2Cl_2) 2935 cm^{-1}; HRMS *m/z* 366.2352 (calcd $C_{28}H_{30}$, 366.2348).

(*E*)-4-Cyclohexyl-1,1,2-triphenyl-1,3-butadiene (7). The reaction mixture was chromatographed using hexanes to afford 49 mg (54%) of the indicated compound as a light yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88-1.30 (m, 5H), 1.53-1.67 (m, 5H), 1.93-1.96 (m, 1H), 5.32-5.38 (dd, *J* = 7.2, 15.6 Hz, 1H), 6.38-6.42 (d, *J* = 15.6 Hz, 1H), 6.84-6.86 (m, 2H), 6.97-7.01 (m, 3H), 7.10-7.19 (m, 5H), 7.25-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.01, 26.16, 32.81, 41.38, 125.88, 126.34, 126.92, 127.30, 127.65, 127.89, 129.77, 131.08, 131.11, 131.53, 139.09, 139.85, 141.03, 141.64, 142.80, 143.26; IR (CH_2Cl_2) 2925, 1422 cm^{-1}; HRMS *m/z* 364.2193 (calcd $C_{28}H_{28}$, 364.2191).

4,4-Dimethyl-2-triphenylvinyl-cyclohex-2-enol (18). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 91.2 mg (24%) of the indicated compound as a light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.80 (m, 11H), 3.90-3.93 (t, *J* = 5.6 Hz, 1H), 5.21 (s, 1H), 6.94-7.33 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.74, 28.21, 29.13, 32.55, 33.41, 66.54, 126.33, 126.42, 126.78, 127.58, 127.71, 128.08, 130.47, 130.65, 131.36, 139.11, 140.76, 141.08, 141.42, 142.69, 143.13, 144.35; IR (CH_2Cl_2) 3300, 2925 cm^{-1}; HRMS *m/z* 380.2145 (calcd $C_{28}H_{28}O$, 380.2140).

Methyl cinnamate (20). This compound was identified by comparing the ^1H and ^{13}C NMR spectra with an authentic sample obtained from Aldrich Chemical Co., Inc.

(*E*)-1-(3-Aminophenyl)-1,2-diphenyl-2-[(4-phenylcyclohexylidene)methyl]ethene (27). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 95 mg (86%) of the indicated compound as a white solid: mp 139-140 °C; ^1H NMR ($CDCl_3$, 400

MHz) δ 0.92-1.03 (m, 1H), 1.38-1.62 (m, 3H), 1.88-1.91 (m, 1H), 2.12-2.18 (m, 1H), 2.27-2.39 (m, 1H), 2.42-2.50 (m, 1H), 2.51-2.56 (m, 1H), 3.41-3.49 (m, 2H), 5.93 (s, 1H), 6.55-6.57 (m, 2H), 6.70-6.72 (d, J = 7.6 Hz, 1H), 6.95-6.98 (m, 2H), 7.04-7.45 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.06, 33.72, 35.65, 44.42, 113.73, 118.07, 122.19, 125.18, 125.98, 126.18, 126.26, 126.95, 127.54, 127.69, 128.35, 128.45, 130.70, 131.55, 137.08, 141.17, 141.23, 142.78, 143.35, 145.01, 145.75, 147.11; IR (CH_2Cl_2) 3461, 3375, 2927, 1617 cm^{-1}; HRMS m/z 441.2464 (calcd $C_{33}H_{31}N$, 441.2457).

(*E*)-1-[(4-Methoxycarbonyl)phenyl]-1,2-diphenyl-2-[(4-phenylcyclohexylidene)methyl]ethene (28). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 73 mg (60%) of the indicated compound as a light yellow solid: mp 137-139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.72-0.76 (m, 1H), 1.36-1.41 (m, 1H), 1.49-1.60 (m, 2H), 1.85-1.89 (m, 1H), 2.12-2.15 (m, 1H), 2.28-2.31 (m, 1H), 2.43-2.47 (m, 1H), 2.49-2.53 (m, 2H), 3.92 (s, 3H), 5.90 (s, 1H), 6.93-6.95 (m, 2H), 7.03-7.05 (m, 2H), 7.08-7.17 (m, 9H), 7.22-7.25 (m, 2H), 7.35-7.37 (m, 2H), 7.95-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.89, 33.60, 35.27, 37.04, 44.25, 52.12, 124.47, 126.01, 126.62, 126.71, 126.85, 127.77, 127.79, 128.25, 128.33, 128.97, 130.56, 131.37, 131.53, 138.79, 140.06, 141.99, 142.02, 142.70, 146.77, 149.10, 167.09; IR (CH_2Cl_2) 2930, 1721 cm^{-1}; HRMS m/z 484.2411 (calcd $C_{35}H_{32}O_2$, 484.2402).

(*E*)-1,2-Diphenyl-2-[(4-phenylcyclohexylidene)methyl]-1-(3-pyridinyl)-ethene (29). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 67 mg (63%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84-0.88 (m, 1H), 1.41-1.50 (m, 2H), 1.63-1.66 (m, 1H), 1.88-1.91 (m, 1H), 2.13-2.16 (m, 1H), 2.30-2.33 (m, 1H), 2.42-2.45 (m, 1H), 2.49-2.55 (m, 2H), 5.92 (s, 1H), 6.93-6.97 (m, 2H), 7.08-

7.14 (m, 10H), 7.16-7.28 (m, 4H), 7.47-7.50 (m, 1H), 8.45-8.47 (m, 1H), 8.61-8.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.98, 33.93, 35.30, 36.96, 44.23, 122.81, 124.28, 126.04, 126.72, 126.79, 126.86, 127.82, 127.90, 128.36, 130.50, 131.45, 137.40, 138.10, 139.02, 139.92, 141.81, 142.31, 142.44, 146.69, 147.55, 152.13; IR (CH_2Cl_2) 2927 cm^{-1}; HRMS *m/z* 427.2305 (calcd $C_{32}H_{29}N$, 427.2300).

(*E*)-1-(3-Furyl)-2-[(4-phenylcyclohexylidene)methyl]-1,2-diphenylethene (30). The reaction mixture was chromatographed using 70:1 hexanes/EtOAc to afford 71 mg (68%) of the indicated compound as a white solid: mp 125-129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19-1.27 (m, 1H), 1.54-1.71 (m, 3H), 1.99-2.02 (m, 1H), 2.27-2.49 (m, 3H), 2.58-2.64 (m, 1H), 6.17 (s, 1H), 6.43-6.44 (m, 1H), 7.01-7.12 (m, 9H), 7.16-7.21 (m, 3H), 7.23-7.31 (m, 3H), 7.37-7.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.16, 33.93, 35.50, 37.15, 44.31, 112.55, 125.35, 126.04, 126.07, 126.45, 126.86, 127.59, 128.22, 128.40, 130.59, 131.73, 136.61, 141.69, 142.35, 142.44, 142.62, 143.75, 146.90; IR (CH_2Cl_2) 2929, 1721 cm^{-1}; HRMS *m/z* 416.2147 (calcd $C_{31}H_{28}O$, 416.2140).

(*E,E*)-1-(4-Chlorophenyl)-1,2-diphenyl-1,3-decadiene (31). The reaction mixture was chromatographed using hexanes to afford 37 mg (37%) of the indicated compound as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81-0.89 (m, 3H), 1.20-1.28 (m, 8H), 1.98-2.03 (q, *J* = 6.8 Hz, 2H), 5.37-5.44 (m, 1H), 6.33-6.37 (d, *J* = 15.6 Hz, 1H), 6.80-6.83 (m, 2H), 6.97-7.00 (m, 3H), 7.08-7.32 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.14, 22.68, 28.91, 29.19, 31.70, 33.22, 126.12, 126.52, 127.41, 127.72, 128.15, 131.04, 131.37, 131.85, 132.44, 132.75, 136.95, 138.33, 139.52, 140.82, 141.24, 142.73; IR (CH_2Cl_2) 2925, 1444 cm^{-1}; HRMS *m/z* 400.1962 (calcd $C_{28}H_{29}Cl$, 400.1958).

(*Z*)-3-Phenyl-2-[(*E*)-2-phenylethenyl]-2,4-pentadien-1-ol (33). The reaction mixture was chromatographed using 4:1 hexanes:EtOAc to afford 29.5 mg (33%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 1H), 4.28 (s, 2H), 6.10-6.15 (d, J = 15.9 Hz, 1H), 7.01-7.06 (d, J = 16.2 Hz, 1H), 7.24-7.58 (m, 16H), 7.67-7.72 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 61.41, 124.71, 126.91, 126.97, 127.14, 127.71, 128.11, 128.20, 128.64, 128.89, 128.99, 129.88, 131.44, 135.41, 135.82, 137.57, 137.85, 139.66, 142.21; IR (CH_2Cl_2) 3370, 2926 cm^{-1}; HRMS *m/z* 338.1677 (calcd $C_{25}H_{22}O$, 338.1671).

(*Z*)-4-Cyclohexylidenemethyl-5-phenyl-4-octene (36). The reaction mixture was chromatographed using hexane to afford 60 mg (85%) of the indicated compound as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.87-0.95 (m, 8H), 1.23-1.30 (m, 6H), 1.37-1.44 (m, 2H), 1.65-1.69 (m, 2H), 1.86 (m, 2H), 2.13-2.18 (dd, J = 7.8, 9.6 Hz, 2H), 2.39-2.44 (t, J = 14.1 Hz, 2H), 5.41 (s, 1H), 7.09-7.22 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.19, 14.48, 21.86, 22.06, 26.77, 26.82, 28.23, 30.12, 35.65, 35.70, 36.83, 123.36, 125.58, 127.41, 129.76, 134.53, 137.46, 139.54, 144.42; IR (CH_2Cl_2) 2955, 1445 cm^{-1}; HRMS *m/z* 282.2350 (calcd $C_{21}H_{30}$, 282.2347).

2-Cyclohexylidenemethyl-2-methyl-1,1-diphenylethene (38a). The reaction mixture was chromatographed using hexanes to afford 64.8 mg (90%) of a 59:41 mixture of two regioisomers. The indicated white solid was recrystallized using hexanes: mp 98-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02-1.04 (m, 2H), 1.38-1.39 (m, 4H), 1.82 (s, 3H), 1.89-2.01 (m, 4H), 5.69 (s, 1H), 7.11-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.27, 26.73, 26.76,

28.11, 30.07, 37.16, 124.11, 126.02, 126.51, 127.47, 128.11, 130.43, 130.82, 132.68, 140.24, 143.65, 143.88; IR (CH_2Cl_2) 2922 cm^{-1}; HRMS *m/z* 288.1883 (calcd $C_{22}H_{24}$, 288.1878).

1-(2,2-Diphenyl-1-methylethenyl)-4-phenylcyclohexene (39a) and 1-[(*E*)-1,2-diphenyl-1-propenyl]-4-phenylcyclohexene (39b). The reaction mixture was chromatographed using hexanes to afford 62.1 mg (71%) of a 56:44 mixture of two regioisomers as a colorless oil. Since the NOESY spectra (see the ^1H NMR spectra) do not provide enough information for the structural assignment, the regioisomers are tentatively assigned according to the general rule for the insertion of alkynes in organopalladium reactions that the vinylic group adds to the less hindered end of the triple bond and the phenyl group from the boronic acid adds to the more hindered end of the triple bond. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50-2.30 (m, 12H), 2.50-2.71 (m, 1H), 5.48 and 5.55 (s, 1H), 7.07-7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.36, 22.55, 28.69, 29.51, 29.77, 30.05, 33.60, 33.67, 39.41, 39.55, 125.59, 125.89, 125.97, 125.99, 126.19, 126.31, 126.53, 126.88, 126.90, 127.52, 127.82, 128.02, 128.07, 128.09, 128.28, 128.35, 129.28, 129.81, 130.08, 133.69, 137.35, 138.15, 139.05, 140.12, 141.84, 142.24, 143.50, 143.91, 145.10, 147.13; IR (CH_2Cl_2) 3046, 2925, 2851 cm^{-1}; HRMS *m/z* 350.2030 (calcd $C_{27}H_{26}$, 350.2034).

(*E*)-1-(4-Methoxycarbonylphenyl)-2-[(4-phenylcyclohexylidene)methyl]-1,4-diphenylbut-1-en-4-yne (40a). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 79 mg (62%) of an 88:12 mixture of two regioisomers. The indicated yellow solid was recrystallized using 20:1 hexanes/EtOAc: mp 102-103 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85-0.91 (m, 1H), 1.44-1.63 (m, 3H), 1.91-1.95 (m, 1H), 2.18-2.37 (m, 3H), 2.50-2.58 (m, 1H), 3.96 (s, 3H), 6.00 (s, 1H), 7.07-7.10 (m, 2H), 7.15-7.29 (m, 8H), 7.33-7.45 (m, 3H), 7.66-7.69 (m, 2H), 7.73-7.76 (d, *J* = 8.4 Hz, 2H), 8.06-8.09 (d, *J* =

8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.56, 33.94, 35.47, 37.58, 44.27, 52.38, 91.86, 93.24, 121.11, 122.98, 123.78, 126.26, 127.00, 128.04, 128.21, 128.23, 128.44, 128.55, 129.00, 129.43, 129.90, 130.22, 131.51, 141.71, 145.03, 145.32, 146.71, 147.25, 167.16; IR (CH_2Cl_2) 2938, 1721 cm^{-1}; HRMS *m/z* 508.2408 (calcd $C_{37}H_{32}O_2$, 508.2402).

(*E,E*)-5,5-Dimethyl-1,3,4-triphenyl-1,3-hexadiene (41a). The reaction mixture was chromatographed using hexanes to afford 50.7 mg (60%) of an 85:15 mixture of two regioisomers. The indicated white solid was recrystallized using hexanes: mp 105-106 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9H), 6.04-6.09 (d, *J* = 16.2 Hz, 1H), 6.72-6.77 (d, *J* = 16.2 Hz, 1H), 6.94-6.99 (m, 1H), 7.07-7.31 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 31.74, 37.79, 125.70, 126.17, 126.54, 127.09, 127.97, 127.98, 128.54, 129.87, 130.10, 131.69, 134.58, 138.42, 144.86, 146.39, 146.46 (one sp^2 carbon was missing due to overlap); IR (CH_2Cl_2) 2922, 1442 cm^{-1}; HRMS *m/z* 338.2039 (calcd $C_{26}H_{26}$, 338.2035); Anal. Calcd. for $C_{26}H_{26}$: C, 92.3; H, 7.7; Found: C, 92.2; H, 7.4.

1-[(*Z*)-1,3,3-Trimethyl-2-phenyl-1-butenyl]-4-phenylcyclohexene (42a). The reaction mixture was chromatographed using hexanes to afford 28.9 mg (35%) of a 95:5 mixture of two regioisomers. The indicated compound was obtained as a yellow wax: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 9H), 1.24-1.44 (m, 1H), 1.87-2.11 (m, 11H), 5.12-5.14 (t, *J* = 2.8 Hz, 1H), 6.89-7.22 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 20.68, 28.51, 29.94, 31.73, 32.98, 35.05, 39.39, 123.32, 125.00, 125.73, 126.61, 126.68, 126.85, 128.21, 129.67, 129.72, 136.65, 142.41, 144.14, 144.74, 147.41; IR (CH_2Cl_2) 2922, 1442 cm^{-1}; HRMS *m/z* 330.2353 (calcd $C_{25}H_{30}$, 330.2348).

(*E,E*)-1,4-Diphenyl-3-(4-nitrophenyl)-1,3-octadiene (43a). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 59.3 mg (62%) of a 86:14 mixture

of two regioisomers. The indicated yellow green solid was recrystallized using 10:1 hexanes/EtOAc: mp 139-140 °C; ^{1}H NMR ($CDCl_3$) δ 0.84-0.89 (t, J = 7.2 Hz, 3H), 1.28-1.36 (m, 2H), 1.54-1.61 (m, 2H), 2.40-2.46 (t, J = 8.1 Hz, 2H), 6.71-6.77 (d, J = 16.2 Hz, 1H), 6.92-6.97 (d, J = 16.2 Hz, 1H), 7.13-7.17 (m, 2H), 7.21-7.26 (m, 1H), 7.28-7.37 (m, 9H), 8.17-8.18 (d, J = 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.12, 23.20, 30.18, 32.36, 123.69, 126.79, 127.70, 127.85, 128.33, 128.44, 128.89, 130.34, 130.74, 131.00, 137.73, 138.73, 140.31, 141.34, 146.71, 150.48; IR (CH_2Cl_2) 2924, 1516 cm^{-1}; HRMS *m/z* 383.1889 (calcd $C_{26}H_{20}NO_2$, 383.1885).

(*E*,*E*)-2-Butyl-1,4-diphenyl-1-(5-pyrimidinyl)-1,3-butadiene (44a). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 51.0 mg (60%) of a 83:17 mixture of two regioisomers. The indicated yellow solid was recrystallized using 10:1 hexanes/EtOAc: mp 55-60 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86-0.91 (t, J = 7.2 Hz, 3H), 1.31-1.38 (m, 2H), 1.56-1.62 (m, 2H), 2.42-2.47 (t, J = 8.1 Hz, 2H), 6.73-6.79 (d, J = 16.2 Hz, 1H), 6.97-6.92 (d, J = 16.2 Hz, 1H), 7.14-7.39 (m, 10H), 8.58 (s, 2H), 9.11 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 23.20, 30.15, 32.55, 126.85, 127.89, 127.99, 128.62, 128.91, 130.77, 130.99, 134.88, 137.55, 140.26, 140.84, 156.98, 157.28; IR (CH_2Cl_2) 3031, 2925, 2860, 1447 cm^{-1}; HRMS *m/z* 340.1944 (calcd $C_{24}H_{24}N_2$, 340.1940).

3-Cyclohexylidenemethyl-4,4-diphenyl-3-buten-2-ol (45a) and (Z)-4-cyclohexylidenemethyl-3,4-diphenyl-3-buten-2-ol (45b). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 73.9 mg (93%) of a 70:30 inseparable mixture of the two regioisomers **45a** and **45b**. Since the NOESY spectra (see the ^{1}H NMR spectra) do not provide enough information for the structural assignment, the regioisomers are tentatively assigned according to the general rule for the insertion of alkynes in

organopalladium reactions that the vinylic group adds to the less hindered end of the triple bond and the phenyl group from the boronic acid adds to the more hindered end of the triple bond. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85-2.04 (m, 14H), 4.50-4.80 (m, 1H), 5.61 and 5.88 (s, 1H), 7.11-7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 22.40, 22.83, 26.62, 26.65, 27.25, 28.05, 28.66, 29.95, 30.29, 37.23, 38.04, 67.54, 68.77, 115.56, 116.38, 123.19, 126.50, 126.95, 126.99, 127.13, 127.49, 127.98, 128.39, 128.40, 128.66, 129.36, 129.82, 129.98, 130.68, 130.75, 138.03, 138.68, 138.81, 140.24, 141.80, 142.33, 143.17, 143.25, 144.87; IR (CH_2Cl_2) 3046, 2925, 2851 cm^{-1}; HRMS *m/z* 318.1988 (calcd $C_{23}H_{26}O$, 318.1984).

2-[(4-Phenylcyclohexylidene)methyl]-3,3-diphenylprop-2-en-1-ol (46a) and (Z)-3-[(4-phenylcyclohexylidene)methyl]-2,3-diphenylprop-2-en-1-ol (46b). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 64.6 mg (85%) of a 68:32 mixture of the two regioisomers **46a** and **46b**. The regioisomers are tentatively assigned according to the general rule for the insertion of alkynes in organopalladium reactions that the vinylic group adds to the less hindered end of the triple bond and the phenyl group from the boronic acid adds to the more hindered end of the triple bond. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.40-2.70 (m, 10H), 4.16 and 4.27 (s, 1H), 5.83 and 5.85 (s, 1H), 7.02-7.27 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 29.90, 30.02, 33.37, 33.98, 35.57, 35.66, 37.10, 37.43, 44.46, 44.61, 64.34, 64.63, 115.59, 120.93, 123.90, 126.16, 126.17, 126.96, 127.05, 127.11, 127.34, 127.40, 127.49, 127.82, 127.84, 128.39, 128.46, 128.47, 128.51, 128.55, 129.29, 129.84, 129.93, 130.02, 130.19, 131.02, 135.19, 141.67, 142.19, 142.62, 143.04, 143.14, 147.07, 147.09; IR (CH_2Cl_2) 3046, 2925, 2851 cm^{-1}; HRMS *m/z* 380.2148 (calcd $C_{28}H_{28}O$, 380.2140).

4,4-Diphenyl-3-[(*E*)-2-phenylethenyl]but-3-en-2-one (47a) and *Z*-3,4-diphenyl-4-[(*E*)-2-phenylethenyl]but-3-en-2-one (47b). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 67.5 mg (71%) of a 63:37 mixture of two regioisomers. The indicated yellow solid was recrystallized using 10:1 hexanes/EtOAc: mp 51-55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 6.51-6.56 (d, J = 16.5 Hz, 1H), 6.87-6.93 (d, J = 16.5 Hz, 1H), 7.18-7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 32.23, 125.56, 126.86, 128.13, 128.43, 128.66, 128.73, 128.84, 130.21, 31.11, 132.39, 137.33, 140.35, 140.60, 141.43, 142.97, 207.87; IR (CH_2Cl_2) 1770 cm^{-1}; HRMS *m/z* 324.1519 (calcd $C_{24}H_{20}O$, 324.1514); Anal. Calcd. for $C_{24}H_{20}O$: C, 88.9; H, 6.2; Found: C, 89.0; H, 6.6.

Ethyl 3,3-diphenyl-2-[(*E*)-2-phenylethenyl]-prop-2-enoate (48a) and *Z*-ethyl 2,3-diphenyl-3-[(*E*)-2-phenylethenyl]-prop-2-enoate (48b). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 54.9 mg (62%) of a 68:32 mixture of two regioisomers. The indicated yellow solid was recrystallized using 10:1 hexanes/EtOAc: mp 84-85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 6.51-6.56 (d, J = 16.5 Hz, 1H), 6.87-6.93 (d, J = 16.5 Hz, 1H), 7.18-7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 32.23, 125.56, 126.86, 128.13, 128.43, 128.66, 128.73, 128.84, 130.21, 31.11, 132.39, 137.33, 140.35, 140.60, 141.43, 142.97, 207.87; IR (CH_2Cl_2) 1730 cm^{-1}; HRMS *m/z* 354.1625 (calcd $C_{25}H_{22}O_2$, 354.1620).

4,4-Diphenyl-3-[(cyclohexylidene)methyl]but-3-en-2-one (49a) and *Z*-3,4-Diphenyl-5-(cyclohexylidene)pent-3-en-2-one (49b). The reaction mixture was chromatographed using 20:1 hexanes:EtOAc to afford 64.4 mg (82%) of the two compounds as a 79:21 inseparable colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25-2.09 (m, 14H), 5.65

and 5.79 (two singlets, 1H), 7.10-7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.28, 26.33, 26.87, 28.09, 28.30, 30.53, 31.06, 31.42, 31.64, 31.85, 37.15, 37.74, 120.55, 122.37, 127.55, 127.68, 127.94, 128.22, 128.26, 128.35, 128.51, 129.18, 130.09, 131.10, 138.79, 139.34, 141.15, 141.67, 141.76, 141.89, 14.43, 144.99, 145.50, 147.15, 206.82, 206.88 (two sp^2 carbon was missing due to overlap); IR (CH_2Cl_2) 1770 cm^{-1}; HRMS *m/z* 316.1831 (calcd $C_{23}H_{24}O$, 316.1827).

***cis*-3,6-Diphenylcyclohexene.** This compound was made from the coupling of iodobenzene, 1,3-cyclohexadiene, and phenylboronic acid. The spectral properties were identical with those previously reported.[24] The spectra data proves the *cis*-configuration of the phenyl groups.

***cis*-6-(4-Methylphenyl)-3-phenylcyclohexene (50).** This compound and the side product 4-methylbiphenyl formed an inseparable mixture. The yield of the compound was determined by GC and NMR spectroscopic analysis.

***cis*-3-(4-Aminophenyl)-6-phenylcyclohexene (51).** The reaction mixture was chromatographed using 4:1 hexanes:EtOAc to afford 55.4 mg (89%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65-1.71 (m, 2H), 1.87-1.96 (m, 2H), 3.26 (br s, 1H), 3.37-3.49 (m, 2H), 5.93 (s, 2H), 6.64-6.69 (m, 2H), 7.08-7.12 (m, 2H), 7.19-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.51, 29.80, 40.51, 41.51, 115.48, 126.31, 128.21, 128.57, 129.02, 130.95, 131.90, 136.32, 144.74, 146.35; IR (CH_2Cl_2) 3372, 2934, 2860, 1624 cm^{-1}; HRMS *m/z* 249.1523 (calcd $C_{18}H_{19}N$, 249.1518).

***cis*-3-(4-Hydroxyphenyl)-6-phenylcyclohexene (52).** The reaction mixture was chromatographed using 5:1 hexanes:EtOAc to afford 43.8 mg (70%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.65-1.75 (m, 2H), 1.93-1.97 (m,

2H), 3.46-3.49 (m, 2H), 4.91 (s, 1H), 5.96 (s, 2H), 6.81-6.83 (d, J = 7.8 Hz, 2H), 7.18-7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 29.45, 29.75, 40.49, 41.42, 115.39, 126.34, 128.17, 128.59, 129.30, 131.19, 131.60, 138.44, 146.20, 154.06; IR (CH_2Cl_2) 3300, 2934 cm^{-1}; HRMS *m/z* 250.1362 (calcd $C_{18}H_{18}O$, 250.1358).

***cis*-3-(4-Methoxyphenyl)-6-phenylcyclohexene (53).** The reaction mixture was chromatographed using 5:1 hexanes:EtOAc to afford 38.3 mg (58%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66-1.72 (m, 2H), 1.93-1.97 (m, 2H), 3.46-3.50 (m, 2H), 3.80 (s, 3H), 5.95 (s, 2H), 6.87-6.90 (m, 2H), 7.21-7.36 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 29.45, 29.73, 55.52, 113.96, 126.31, 128.15, 128.56, 129.07, 131.13, 131.61, 138.25, 146.20, 158.20; IR (CH_2Cl_2) 2860 cm^{-1}; HRMS *m/z* 264.1520 (calcd $C_{19}H_{20}O$, 264.1514).

***cis*-3-(2-Methylphenyl)-6-phenylcyclohexene (55).** The reaction mixture was chromatographed using 5:1 hexanes:EtOAc to afford 11.8 mg (19%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43-1.70 (m, 2H), 1.91-1.98 (m, 2H), 2.38 (s, 3H), 3.49-3.50 (m, 1H), 3.68-3.71 (m, 1H), 5.92-6.01 (m, 2H), 7.13-7.37 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 19.54, 27.69, 29.41, 37.27, 41.56, 126.12, 126.31, 126.36, 127.99, 128.15, 128.62, 130.64, 131.53, 131.59, 135.83, 143.83, 146.29; IR (CH_2Cl_2) 2930 cm^{-1}; HRMS *m/z* 248.1570 (calcd $C_{19}H_{20}$, 248.1565).

***cis*-6-(4-Aminophenyl)-3-(2-methylphenyl)cyclohexene (56).** The reaction mixture was chromatographed using 4:1 hexanes:EtOAc to afford 47.3 mg (72%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63-1.65 (m, 2H), 1.90-1.94 (m, 2H), 2.39 (s, 3H), 3.40-3.41 (m, 1H), 3.68-3.69 (m, 1H), 5.88-5.98 (m, 2H), 6.68-6.70 (m,

2H), 7.11-7.37 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 19.53, 27.63, 29.62, 37.33, 40.65, 115.46, 126.08, 126.23, 127.97, 128.94, 130.58, 131.11, 132.14, 135.82, 136.45, 144.00, 144.75; IR (CH_2Cl_2) 3372, 2935 cm^{-1}; HRMS *m/z* 263.1680 (calcd $C_{19}H_{21}N$, 263.1674).

***cis*-6-(4-Aminophenyl)-3-(4-chlorophenyl)cyclohexene (57).** The reaction mixture was chromatographed using 4:1 hexanes:EtOAc to afford 37.6 mg (53%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60-1.65 (m, 2H), 1.89-1.94 (m, 2H), 3.39-3.44 (m, 2H), 5.88-5.98 (m, 2H), 6.66-6.69 (m, 2H), 7.06-7.09 (m, 2H), 7.21-7.31 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 29.22, 29.75, 40.30, 40.59, 117.36, 128.48, 128.92, 129.28, 130.59, 131.72, 131.84, 144.42 (two sp^3 carbons were missing due to overlap); IR (CH_2Cl_2) 3372, 2945 cm^{-1}; HRMS *m/z* 283.1134 (calcd $C_{18}H_{18}ClN$, 283.1128).

***cis*-3-Phenyl-6-[(4-phenylcyclohexylidene)methyl]cyclohexene (58).** The reaction mixture was chromatographed using 4:1 hexanes:EtOAc to afford 72.2 mg (88%) of the indicated compound as an orange oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51-1.60 (m, 3H), 1.69-1.75 (m, 2H), 1.92-1.99 (m, 4H), 2.22-2.33 (m, 2H), 2.66-2.81 (m, 2H), 3.11-3.13 (m, 1H), 3.14 (s, 1H), 5.15-5.18 (d, J = 6.3 Hz, 1H), 5.74-5.76 (d, J = 9.0 Hz, 1H), 7.16-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.82, 27.30, 28.80, 28.84, 29.90, 33.31, 33.35, 35.35, 35.43, 35.93, 36.93, 41.03, 44.84, 44.87, 125.97, 216.05, 126.91, 126.93, 128.05, 128.29, 128.39, 129.22, 132.33, 132.74, 138.06, 138.08, 146.18, 147.06; IR (CH_2Cl_2) 2950 cm^{-1}; HRMS *m/z* 328.2200 (calcd $C_{25}H_{28}$, 328.2191).

Acknowledgement. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society for partial support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. for donations of $Pd(OAc)_2$.

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Chapter 2. Synthesis of Substituted Quinolines by the Electrophilic Cyclization of *N*-(2-Alkynyl)anilines

Based on a paper to be submitted to the *Journal of Organic Chemistry*

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Abstract

A wide variety of substituted quinolines have been readily synthesized under mild reaction conditions by the 6-*endo*-dig electrophilic cyclization of *N*-(2-alkynyl)anilines by ICl, I_2, Br_2, PhSeBr and *p*-$NO_2C_6H_4SCl$. The reaction affords 3-halogen-, selenium- and sulfur-containing quinolines in moderate to good yields in the presence of various functional groups. Analogous quinolines bearing a hydrogen in the 3-position have been synthesized by the $Hg(OTf)_2$-catalyzed ring closure of these same alkynylanilines.

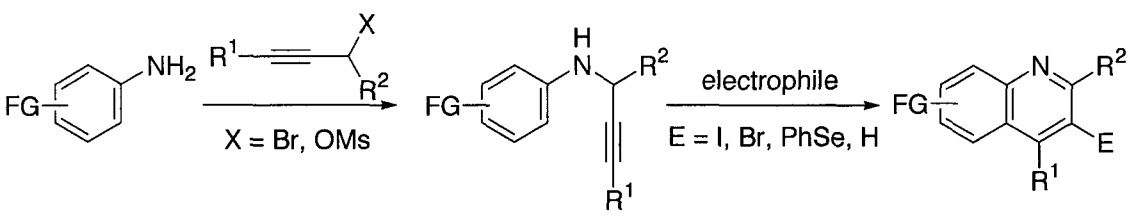
Introduction

The quinoline skeleton occurs in numerous natural products, especially in alkaloids.[1] Many quinolines display interesting physiological activities and have found applications as pharmaceuticals (e.g., antimalarial drugs, such as quinine or chloroquine) and agrochemicals, as well as being general synthetic building blocks.[2] Halogen-containing quinolines are of significant interest because the halogen atom sometimes plays a crucial role in the compound's bioactivity and provides an avenue for further structural elaboration.[3] The

isolation and synthesis of naturally-occurring quinoline derivatives have received considerable attention in the literature due to their biological and pharmaceutical importance.[4] Although simple 3-bromoquinolines can be obtained by the bromination of quinoline hydrochlorides,[5] the site-selective aromatic halogenation of substituted quinolines remains a synthetic challenge.[6] 3-Haloquinolines have also been synthesized by a photochemical method,[7] a modified Skraup quinoline synthesis employing halo-substituted acroleins and anilines,[8] and the Friedländer quinoline synthesis.[3c] Some of these methods suffer relatively low yields, poor regioselectivity, and/or rather lengthy synthetic sequences.

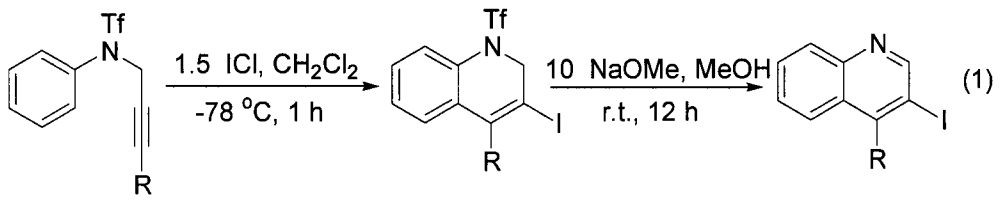
The cyclization of alkynes containing proximate nucleophilic centers promoted by electrophiles is currently of great interest and developing into a very effective strategy for carbo- and heterocyclic ring construction. This chemistry provides a convenient approach to the synthesis of functionalized cyclic compounds through the *regioselective* addition of a nucleophile and the electrophile across the carbon-carbon triple bond. Successful examples of this process have been reported for the synthesis of isoquinolines,[9] benzothiophenes,[10] polycyclic aromatics,[11] indoles,[12] naphthalenes,[13] furopyridines,[14] isoindolin-1-ones,[15] isocoumarins[16] and isochromenes.[17] However, no one has thus far employed this chemistry to synthesize quinolines. Preliminary studies on this project have previously been communicated.[18] Herein, we wish to report the full details of this successful strategy for the synthesis of quinolines using very mild reaction conditions (Scheme 1).

Scheme 1



Results and Discussion

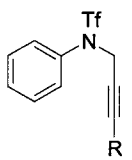
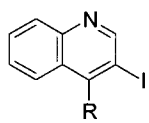
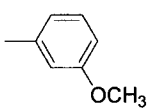
During our early efforts to obtain 3-iodoquinolines, a two-step procedure was first examined (eq 1). Triflamide **1** with R = Ph was treated with ICl at -78 °C to afford a hydroquinoline intermediate, which could be subsequently treated with base to achieve

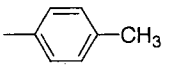
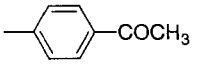
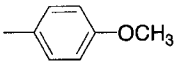
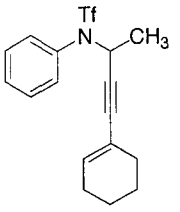
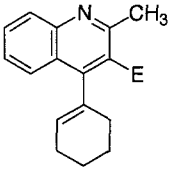
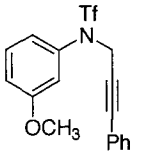
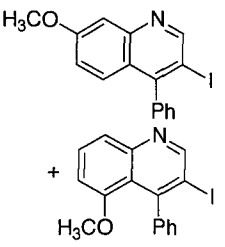
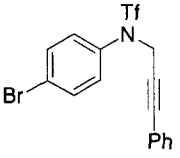
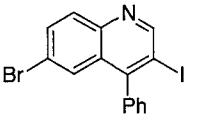
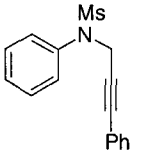
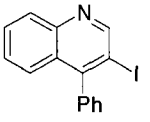


(1)

aromaticity.[19] 3-Iodo-4-phenylquinoline (**2**) was generated in a good yield using this method (entry 1, Table 1). The cyclization of methanesulfonamide **20** was also successful (entry 11, Table 1). Obviously, one can obtain hydroquinolines after the first step without further base-induced deprotection of the nitrogen. Thus, we have employed the reaction conditions developed here on a wide variety of other substrates and the results are summarized in Table 1.

Table 1. Synthesis of Quinolines from *N*-(2-Alkynyl)triflamides[a]

entry	triflamide	electrophile	product	overall % yield
				
1	R = Ph **1**	ICl	**2**	88
2	R =  **3**	ICl	**4**	62

3	R = 	**5**	ICl		**6**	45
4	R = 	**7**	ICl		**8**	51
5	R = 	**9**	ICl		**10**	trace
6			$I_2/AgClO_4$		**10**	trace
7	R = *n*-Bu	**11**	ICl		**12**	25
8		**13**	ICl		**14**	trace
9		**15**	ICl		**16** + **17**	60 + 25
10		**18**	ICl		**19**	56
11		**20**	ICl		**2**	74

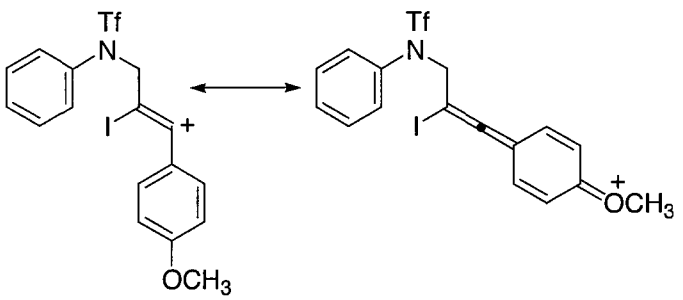
[a] All reactions were run using 0.30 mmol of the *N*-(2-alkynyl)triflamide and 1.5 equiv of ICl in 3 mL of CH_2Cl_2 at -78 ^{o}C for 1 h. After work-up, the solvent was removed, the crude mixture and 10 equiv of NaOMe were directly dissolved in MeOH and stirred overnight.

Good yields have been obtained when the group R on the alkyne is phenyl, as well as relatively electron-rich or electron-deficient aryl groups (entries 1-4, Table 1). The cyclization of substrates bearing both electron-donating and -withdrawing groups on the

aniline moiety proved no difficulty when R is phenyl group (entries 9 and 10). When 3-methoxyaniline **15** was utilized, two isomeric quinoline products were obtained. The product formed from cyclization onto the less sterically hindered *para* position of the methoxy group is the major isomer. Although this is a convenient and new approach to 3-iodo-1,2-dihydroquinolines, the failure of the reactions with substrates **9** and **13** and the poor yield from the reaction of the alkyl-substituted alkyne **11** encouraged us to search for a more general and straightforward synthetic approach to iodoquinolines.

The products of addition of ICl to the triple bond of amides **9** and **13** were the major products observed under the above reaction conditions. These presumably are generated from the relatively stable cations, formed by the electron-releasing MeO or vinylic groups, followed by trapping by the chloride anion generated from the ICl (Scheme 2). It appears that the relatively stable iodovinylic cation is reluctant to undergo

Scheme 2

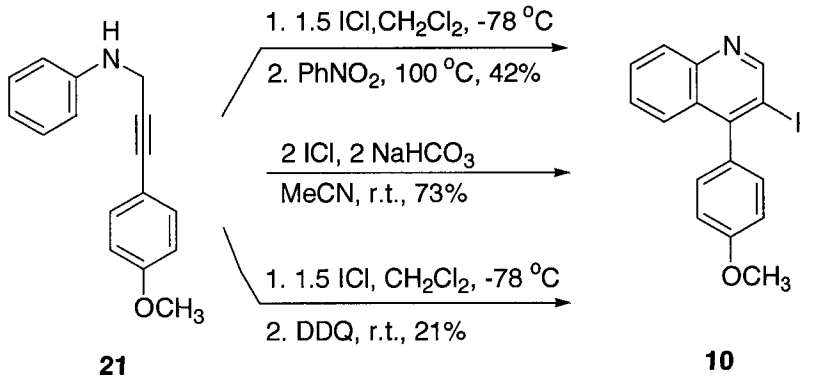


electrophilic attack on the *N*-substituted aromatic ring. Therefore, removal of the trifluoromethanesulfonyl group might be expected to increase the nucleophilicity of the aromatic ring and thus improve the yield of the desired cyclization.

Aniline derivative **21** was thus subjected to direct electrophilic cyclization (Scheme 3). A fair amount of the iodoquinoline **12** was generated upon reaction with ICl and

subsequent treatment by an oxidizing agent. It was later found that the oxidation step was unnecessary, since **10** was formed in a good yield upon iodination with ICl plus $NaHCO_3$ without subsequent addition of an oxidant.

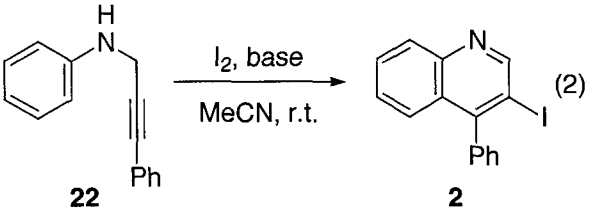
Scheme 3



21 **10**

We then optimized the reaction of aniline **22** using I_2 in the presence of various bases (eq 2). The results are summarized in Table 2. When a mixture of aniline **22**, 3 equiv of I_2 and 2 equiv of $NaHCO_3$ in MeCN was stirred at r.t. for 0.5 h, the desired iodoquinoline **2** was obtained cleanly in a 76% yield (entry 1, Table 2). This reaction has also been run on a 2.0 mmol scale and product **2** was generated in a 75% yield, indicating the utility of this procedure on a large scale. A much longer reaction time was required when decreasing the amount of I_2 from 3 to 2 equiv (entry 2, Table 2). Essentially the same yield was obtained when using either 3 or 6 equiv of I_2 (compare entries 1 and 3, Table 2). Thus, we chose to use 3 equiv of I_2 in the rest of our optimization work. The reaction was also dramatically slowed down when there was no base employed, even in the presence of 6 equiv of I_2 (entry 4, Table 2). Other carbonate bases, such as Cs_2CO_3 and $NaOCO_2CH_3$, which have been successfully employed in our isoquinoline synthesis,[9] gave a yield comparable to that of $NaHCO_3$ (entries 5 and 6). Organic bases, namely triethylamine and pyridine, didn't

improve the yield either (entries 7 and 8). The combination of 0.30 mmol of the *N*-(2-alkynyl)aniline, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN at room temperature was therefore chosen as our "optimal" reaction conditions and the scope of this reaction was systematically investigated (Table 3).



22 **2**

Table 2. Effect of I_2 Stoichiometry and Base on the Cyclization of *N*-(3-Phenyl-2-propynyl)aniline 22[a]

entry	equiv of I_2	base (equiv)	% yield
1	3	$NaHCO_3$ (2)	76
2	2	$NaHCO_3$ (2)	44[b]
3	6	$NaHCO_3$ (2)	75
4	6	-	56[c]
5	3	$NaOCO_2CH_3$ (2)	72
6	3	Cs_2CO_3	71
7	3	pyridine (2)	35
8	3	Et_3N (2)	45

[a] All reactions were run under the following conditions unless otherwise stated: 0.3 mmol of **22**, I_2 and the base in 3 mL of MeCN were stirred at room temperature for 12 h. [b] The reaction wasn't finished after 24 h; 40% of **22** was left. [c] After 24 h, 25% of **22** was left.

First, various substituents on the end of the alkyne were examined. In general, electron-rich and electron-deficient aryl groups have generated quinolines in good to excellent yields, presumably because these substitutents are capable of stabilizing a vinylic cation intermediate (entries 1, 5, and 10; Table 3). The yield dropped and a much longer reaction time was needed for the *p*-acetylphenyl-substituted alkyne **30** to react (24 h *vs.* 0.5 h for alkyne **22**) (entry 11). Substrate **31** with a strong electron-withdrawing

Table 3. Synthesis of Quinolines by Electrophilic Cyclization of *N*-(2-Alkynyl)anilines

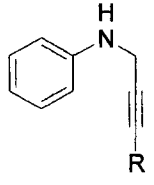
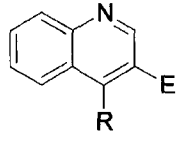
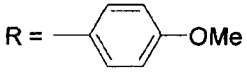
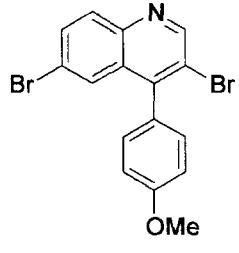
entry	propargylic aniline		electrophile	product(s)		% yield
						
				E		
1	R = Ph	**22**	I_2[a]	I	**2**	76
2			ICl[b]	I	**2**	83
3			PhSeBr[b]	PhSe	**23**	20
4			NBS[b]	Br	**24**	0[c]
5	R = 	**21**	I_2[a]	I	**10**	71
6			ICl[b]	I	**10**	73
7			PhSeBr[b]	PhSe	**25**	74
8			Br_2[b]		**26**	51

Table 3. Continued

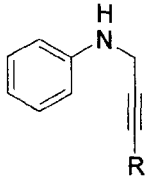
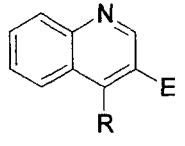
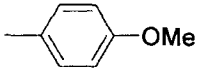
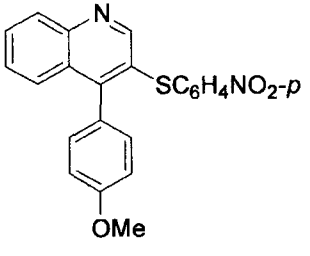
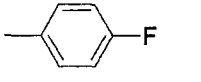
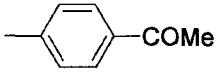
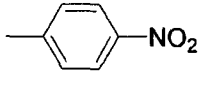
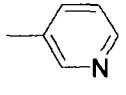
entry	propargylic aniline	electrophile	product(s)		% yield
					
			E		
9	R = 	**21** p-$O_2NC_6H_4SCl$[b]		**27**	12
10	R = 	**28** I_2[a]	I	**29**	78
11	R = 	**30** I_2[a,d]	I	**8**	57
12	R = 	**31** I_2[a]	I	**32**	trace
13	R = 	**33** I_2[a]	I	**34**	25

Table 3. Continued

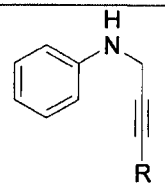
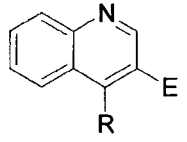
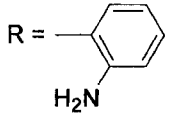
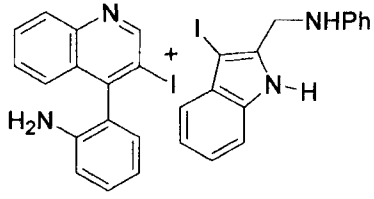
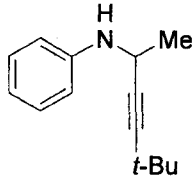
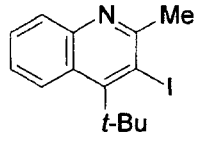
entry	propargylic aniline		electrophile	product(s)			% yield
					E		
14	R = 	**35**	I_2[a]		I	**36** + **37**	55 + 0
15	R = *n*-Bu	**38**	I_2[a]		I	**12**	43[e]
16			ICl[b]		I	**12**	30
17	R = $SiMe_3$	**39**	I_2[a]		I	**40**	trace
18	R = H	**41**	I_2[a]		I	**42**	0
19		**43**	I_2[a]			**44**	0

Table 3. Continued

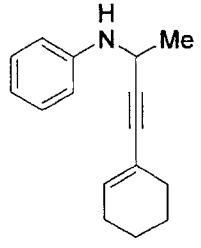
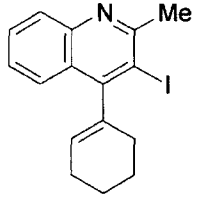
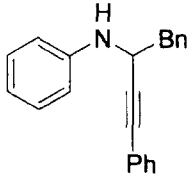
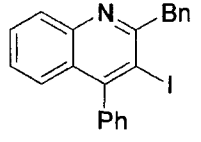
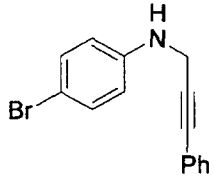
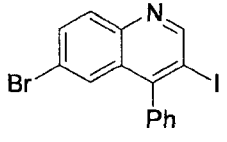
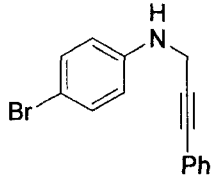
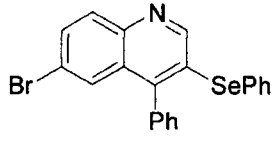
entry	propargylic aniline		electrophile	product(s)		% yield
20		**45**	I_2[a]		**14**	80
21		**46**	I_2[a]		**47**	38[f]
22		**48**	I_2[a]		**19**	63
23		**48**	PhSeBr[b]		**49**	75

Table 3. Continued

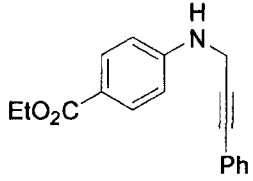
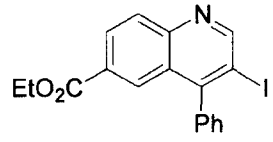
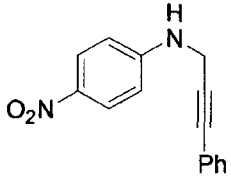
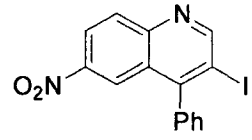
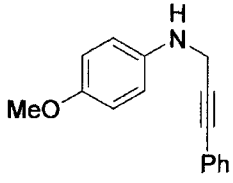
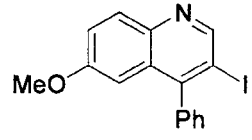
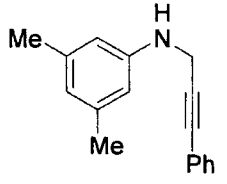
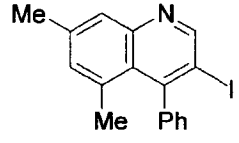
entry	propargylic aniline		electrophile	product(s)			% yield
24		**50**	I_2[a]		I	**51**	88
25			PhSeBr[b]		PhSe	**52**	56
26		**53**	I_2[a]			**54**	79
27		**55**	I_2[a]			**56**	75
28		**57**	I_2[a]			**58**	58[d]

Table 3. Continued

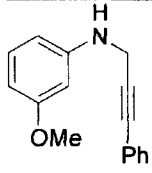
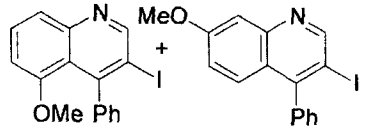
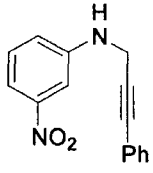
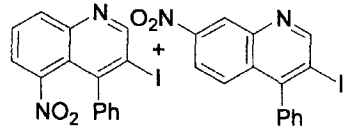
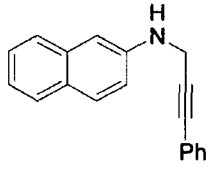
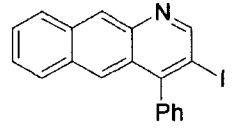
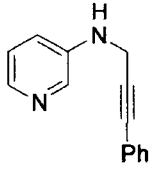
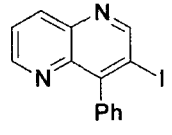
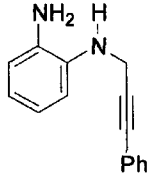
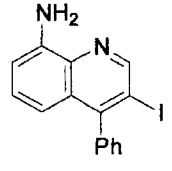
entry	propargylic aniline		electrophile	product(s)		% yield
29		**59**	I_2[a]		**16 + 17**	29 + 37
30		**60**	I_2[a]		**61 + 62**	71 + 8
31		**63**	I_2[a]		**64**	75
32		**65**	I_2[a]		**66**	trace
33		**67**	I_2[a]		**68**	0

Table 3. Continued

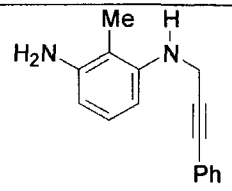
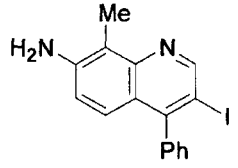
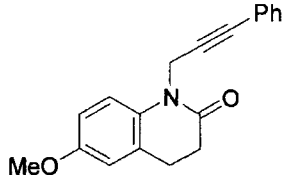
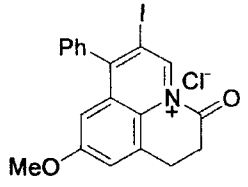
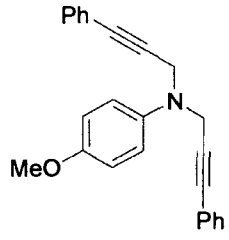
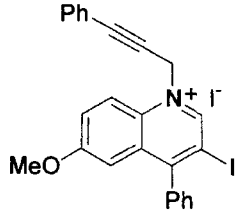
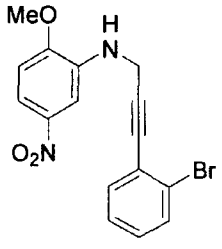
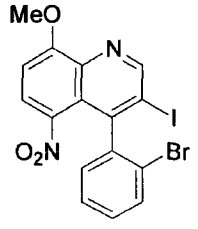
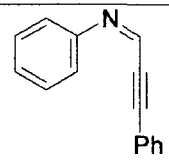
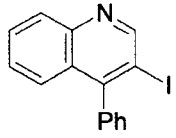
entry	propargylic aniline		electrophile	product(s)		% yield
34		**69**	I_2[a]		**70**	35[g]
35		**71**	ICl[h]		**72**	50
36		**73**	I_2[a]		**74**	62
37		**75**	I_2[a]		**76**	80

Table 3. Continued

entry	propargylic aniline	electrophile	product(s)		% yield
38		77	I_2[a]		**2**	0

[a] All reactions were run under the following conditions unless otherwise stated: 0.3 mmol of the propargylic aniline, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of MeCN were stirred at room temperature for 0.5 h. [b] Two equiv of ICl/PhSeBr/Br_2/NBS/*p*-$O_2NC_6H_4SCl$ in 1 mL of MeCN was added dropwise to the solution of 0.3 mmol of propargylic aniline and 2 equiv of $NaHCO_3$ in 2 mL of MeCN over 10 min at r.t. and the solution was stirred for another 10 min. [c] Only the product formed from bromination of the 4-position of the aniline ring was obtained. [d] The reaction took 24 h. [e] The product was obtained together with a 26% yield of 3,6-diiodoquinoline. [f] Compound **2** was also generated in a 25% yield. [g] 3,6-Diiodoquinoline was also obtained in a 28% yield. [h] ICl (4 equiv) in 1 mL of CH_2Cl_2 was added dropwise to the solution of 0.30 mmol of **71** in 2 mL of CH_2Cl_2 over 10 min at -78 °C and the solution was stirred for another 10 min.

NO_2 group on the *para*-position of the arene failed to generate the cyclization product (entry 12). The yield of the pyridine derivative **34** also suffers, which might be the result of the coordination of I^+ to the nitrogen of the pyridine, further lowering the electron density of the pyridine ring (entry 13).[9] Interestingly, an amino group, generally believed to be a stronger nucleophile than a phenyl group, *ortho* to the alkynyl moiety remains untouched during the cyclization in contrast to our previously reported indole synthesis employing 2-(1-alkynyl)anilines (entry 14).[12a] This indicates the need for an appropriate leaving group on the nitrogen in order to effect a successful indole synthesis. Substitution on the alkyne of a vinylic group presents no problem as the 4-(1-cyclohexenyl)quinoline **14** was formed cleanly in an 80% yield (entry 20). In fact, cyclization by I_2 proceeded in decent yield even when the terminus of the carbon-carbon triple bond bore an alkyl group. Thus, 4-butyl-3-iodoquinoline (**12**) can be synthesized in a 43% yield alongside a 26% yield of 4-butyl-3,6-diiodoquinoline, which is presumably formed by iodocyclization of intermediate *N*-(2-heptynyl)-4-iodoaniline formed by prior iodination of the aniline (entry 15, Table 3). The desired cyclization did not occur when the acetylene bore a sterically-hindered silyl or *t*-Bu group, or a simple H atom on the triple bond (entries 17-19). The 2,3,4-trisubstituted quinoline **47** was obtained in a moderate yield, together with iodoquinoline **2**, which most likely is generated from elimination of toluene during the aromatization step (entry 21). Thus, a 63% overall yield was obtained when a benzyl group was introduced on the carbon between the nitrogen and the triple bond (entry 21).

An interesting feature of this cyclization is the fact that the yields aren't significantly affected by the substituents on the aniline ring. *para*-Substituents ranging from a weak electron-withdrawing group, like a Br, to a strong electron-withdrawing group, like a NO_2,

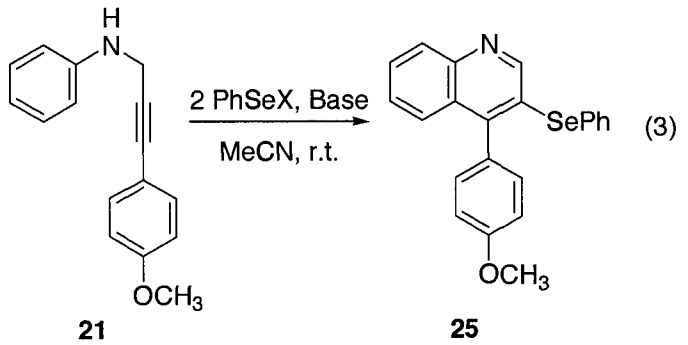
along with an electron-donating MeO group, all generated the corresponding substituted quinoline derivatives in good yields (entries 22, 24, 26 and 27). A substrate with two methyl groups situated *meta* to the amino group also afforded a high yield of the corresponding quinoline, although a longer reaction time was needed (entry 28).

The regioselectivity of this cyclization has also been investigated. 3-Methoxyaniline **59** afforded the *ortho*-cyclization regioisomer **16** and the *para*-cyclization isomer **17** in 29% and 37% yields respectively (entry 29). On the other hand, very interestingly, the 3-nitroaniline **60** afforded regioisomers **61** and **62** in a 79% combined yield with cyclization occurring primarily *ortho* to the nitro group (9:1 ratio of *ortho* to *para* cyclization) for reasons that are not obvious now (entry 30). Excellent regioselectivity was achieved in the cyclization of 2-naphthylamine **63**, since only one isomer was observed. The ring closure occurred selectively in the less sterically-hindered 3-position of the naphthalene ring (entry 31). Unfortunately, cyclization onto a pyridine ring proved unsuccessful using our current reaction conditions (entry 32).

Other halogen electrophiles have also been successfully employed in this quinoline synthesis. The stronger electrophile ICl has also been employed in this cyclization. Our "optimal" ICl reaction conditions are: 0.30 mmol of the propargylic aniline, 2 equiv of ICl, and 2 equiv of $NaHCO_3$ in 3 mL of MeCN are stirred at room temperature. 3 Equiv of ICl were not necessary, since all of the alkynes were completely consumed when 2 equiv of ICl were employed. Lowering the temperature to 0 °C or -78 °C did not improve the yields. Yields comparable to those obtained using I_2 (compare entry 1 with 2, and entry 5 with 6, Table 3) have been obtained, but the reactions are much faster, being completed in about 5 min. However, using ICl as the electrophile was not helpful in improving the yields of the

desired monoiodinated quinolines where I_2 only generated a moderate yield as in entries 15 and 16. When 2 equiv of NBS in MeCN was added dropwise to the mixture of aniline **22** and 2 equiv of $NaHCO_3$ in MeCN, *N*-(3-phenyl-2-propynyl)-4-bromoaniline was obtained in quantitative yield, and no cyclization to the quinoline was observed after 2 h. The reaction of Br_2 with alkynylaniline **22** was very messy with the formation of mono-, di- and tribromoquinolines evident. In the case of aniline **21**, we were able to isolate dibromoquinoline **26** in a 51% yield (entry 8, Table 3).

Although PhSeCl have been found to be an effective electrophile in our electrophilic cyclization of alkynes to isoquinolines,[9] isochromenes,[17] isocoumarins,[16] benzo[*b*]thiophenes[10] and isoindolin-1-ones,[15] it has not been nearly as effective in this process (entry 1, Table 4). No reaction occurred when using PhSeSePh (entry 2, Table 4). But interestingly, when PhSeBr was used as the electrophile, the desired 3-(phenylselenyl)quinoline **25** was obtained in a 74% yield (entry 3, Table 4). Surprisingly, simply changing the base from $NaHCO_3$ to Na_2CO_3 resulted in a messy reaction and none of the desired quinoline **25** was observed (entry 4, Table 4). Organic bases, such as NEt_3 and pyridine, provided lower yields (entries 5 and 6, Table 4). The presence of base to remove the side product HBr is crucial (entry 7, Table 4). The reaction of **21** and PhSeBr without any base afforded none of desired quinoline. Instead, a 42% yield of aniline **21** with a PhSe group *para* to the aniline nitrogen was obtained. It is important to emphasize that the dropwise addition of ICl and PhSeBr to the reaction vessel is very important in obtaining a clean reaction, but this is unnecessary when using I_2. Representative examples of the synthesis of selenium-containing quinolines are included in entries 3, 7, 23 and 25 in Table 3.



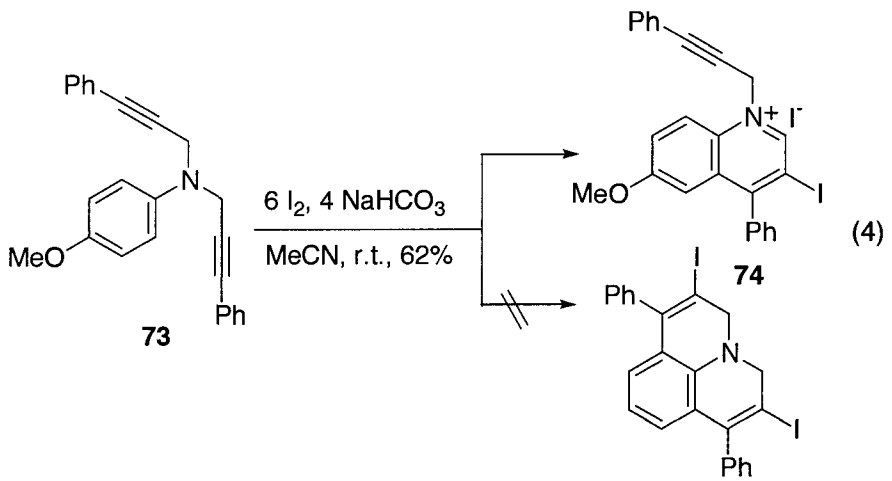
(3)

Table 4. Effect of Organoselenium Electrophiles on the Cyclization of Aniline 21 (eq 3)[a]

entry	eletrophile	base (equiv)	% yield of **25**
1	PhSeCl	$NaHCO_3$ (2)	38[b]
2	PhSeSePh	$NaHCO_3$ (2)	0
3	**PhSeBr**	**$NaHCO_3$ (2)**	**74**
4	PhSeBr	Na_2CO_3 (1)	0
5	PhSeBr	NEt_3 (3)	40
6	PhSeBr	Pyridine (3)	48
7	PhSeBr	-	0[c]

[a] 2 Equiv of PhSeX in 1 mL of MeCN was added dropwise to the solution of 0.3 mmol of propargylic aniline and base in 2 mL of MeCN at r.t. [b] A 19% yield of 3,6-di(phenylselenyl)quinoline was also obtained. [c] Compound **21** bearing a PhSe group *para* to the amino group was obtained in a 42 % yield.

When *N*, *N*-disubstituted anilines were employed in the reaction with ICl or I_2 quinolinium salts can be obtained (eq 4 and entries 35 and 36, Table 3).



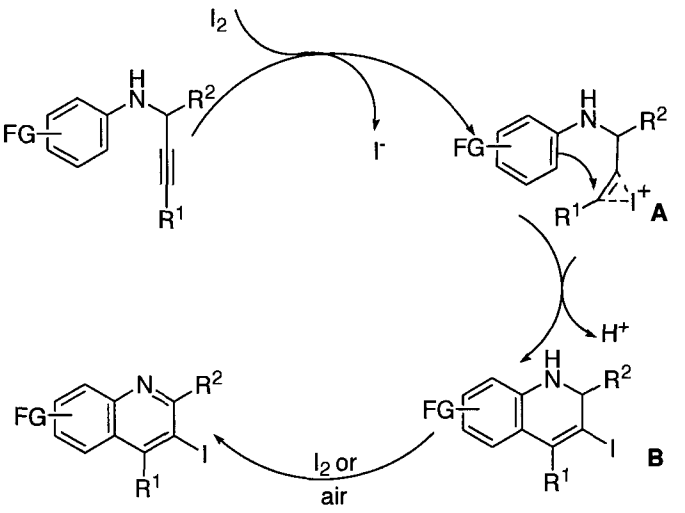
(4)

An analogous approach to quinolines might be to cyclize *N*-(3-phenyl-2-propynylidene)aniline, which can be easily generated by the condensation of aniline with 3-

phenylpropynal. However, under our standard I_2 reaction conditions, none of the desired iodoquinoline **2** was generated. Instead, the imine starting material decomposed (entry 38, Table 3).

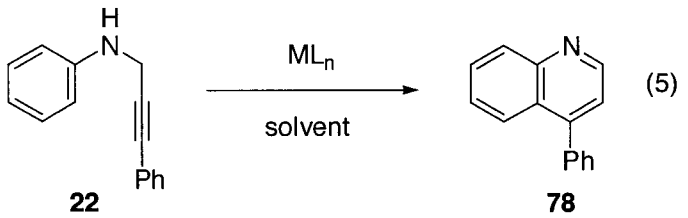
We propose the following mechanism for this iodocyclization process: (1) the carbon-carbon triple bond of the propargylic aniline coordinates to the iodine cation generating an iodonium intermediate **A**, (2) intramolecular nucleophilic attack of the aromatic ring of the aniline on the activated triple bond forms dihydroquinoline **B**, (3) in the presence of I_2 or ICl, the dihydroquinoline **B** is oxidized to the corresponding quinoline[20] (Scheme 4). It is also possible that the dihydroquinoline is not oxidized to the quinoline until it is exposed to air during the work-up.

Scheme 4



Recently, considerable attention has focused on metal catalysts which can effectively activate unsaturated bonds towards intramolecular electrophilic attack on arenes. Various heterocycles and carbocycles have been successfully synthesized using this strategy.[21-26] However, the direct cyclization of simple propargylic anilines to quinolines has not yet been

achieved. Our interest in the synthesis of quinolines bearing a hydrogen in the 3 position encouraged us to first screen those reagents and catalysts previously reported to be active in this kind of chemistry. The results are summarized in Table 5.



22 **78**

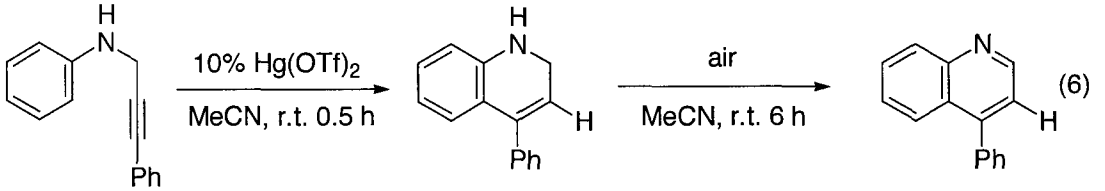
Table 5. Metal-Catalyzed Cyclization of Aminoalkyne 22

entry	catalyst	solvent	temp. (°C)	time (h)	yield of **78** (**22**)	ref
1	5% $AuCl_3$	EtOH	75	48	10 (75)	21
2	5% $AuCl_3$/15% AgOTf	MeCN	70	72	15 (70)	22
3	5% $RuCl_3$/10% AgOTf	$ClCH_2CH_2Cl$	65	48	8 (90)	23
4	5% $PtCl_4$	$ClCH_2CH_2Cl$	70	48	38 (51)[a]	24
5	5% $PtCl_2$	toluene	80	48	5 (80)	25
6	3% $Cu(OTf)_2$	CH_2Cl_2	r.t.	48	0	
7	3% $Hg(O_2CCF_3)_2$	MeCN	r.t.	48	trace	
8	5% $Hg(OTf)_2$/ 15% TMU	MeCN	r.t.	24	55 (35)[a]	26
9	5% $Hg(OTf)_2$	MeCN	r.t.	48	50 (45)[a]	
10	3% $Hg(OTf)_2$	MeCN	50	168	40 (50)[a]	
11	4% $Hg(OTf)_2$	DMSO	100	48	10 (71)	
12	5% $Hg(OTf)_2$/ 1.2 MnO_2	MeCN	r.t.	24	< 1	
13	**10% $Hg(OTf)_2$**	**MeCN**	**r.t.**	**6**	**96**	
14	10% $Hg(OTf)_2$	CH_2Cl_2	r.t.	24	95	

[a] The yield didn't improve when the reaction was run a longer time.

$AuCl_3$ which has been shown to be an effective catalyst for the cyclization of imines derived from carbonyl compounds and propargylic amines[21] and the hydroarylation of alkynes[22] was ineffective in this quinoline process (entries 1 and 2, Table 5). The reaction of aniline and 3-phenylpropynal was messy under the reaction conditions of entry 1. Unsatisfactory results were also obtained from $RuCl_3$/AgOTf, $PtCl_2$, and $PtCl_4$ salts, although

they have been shown to effect the cyclization of *N*-protected anilines to hydroquinolines (entries 3-5).[23-25] $Hg(OTf)_2$ was later found to be the catalyst of choice, while both $Cu(OTf)_2$ and $Hg(O_2CCF_3)_2$ are inactive (entries 6-8). Thus, 10% $Hg(OTf)_2$ can promote the cyclization of **22** to quinoline **78** in a 96% yield using either MeCN or CH_2Cl_2 as the solvent at r.t. (entries 13 and 14). Lowering the amount of $Hg(OTf)_2$ or changing the solvent or addition of an oxidant are all detrimental to the reaction (entries 8-12). This reaction is believed to proceed in a stepwise manner, because compound **79** could be separated from the reaction mixture after half an hour and it was gradually converted to compound **78** when stirred in the presence of air, but the absence of mercury salts (eq 6). However, analogous dihydroquinoline intermediates have not been observed in the iodine-promoted ring closure process (Table 3).

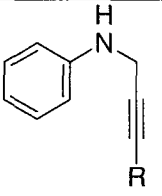
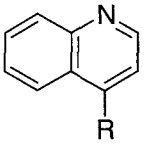
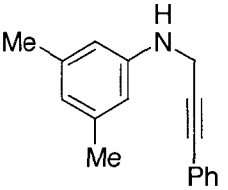
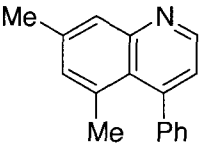


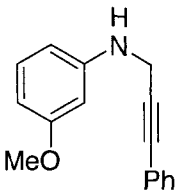
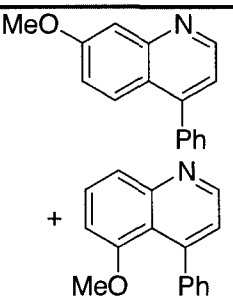
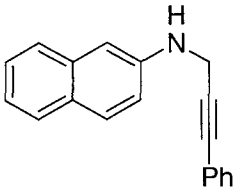
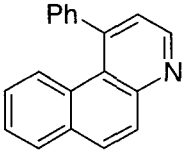
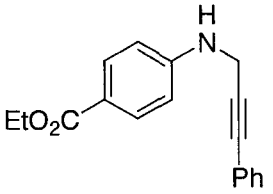
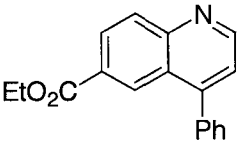
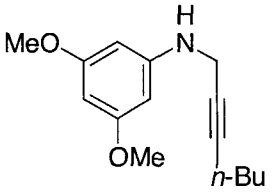
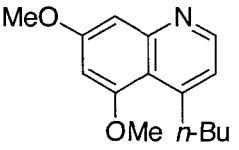
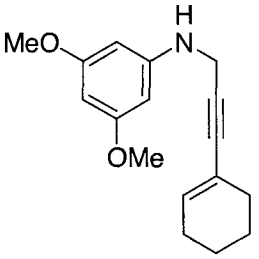
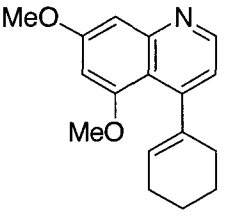
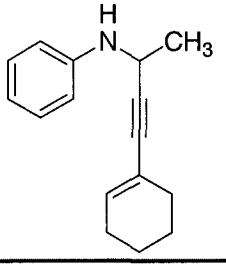
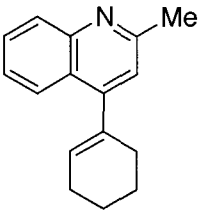
22 **79** **78**

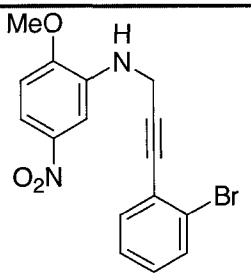
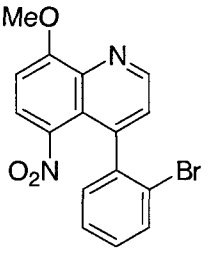
The scope of this metal-catalyzed process using the above "optimal" reaction conditions was subsequently examined. The compatibility of substrates is very similar to that of the I_2 cyclization process. With phenyl and *p*-$MeOC_6H_4$ groups on the end of the alkyne, the desired quinolines were generated in excellent yields (entries 1 and 2, Table 6). An analogous 3,5-dimethylaniline derivative was also cyclized in good yield (entry 4, Table 6). Only 4% $Hg(OTf)_2$ was needed for the cyclization of substrate **59** with a *meta*-methoxy substituent (entry 5, Table 6). Regioisomers **83** and **84** were obtained in a 73% overall yield. The yield of isomer **84** is slightly higher than that of **83**, indicating the cyclization is under

kinetic control. On the other hand, cyclization of the 2-naphthyl derivative **63** afforded a high yield of a single product in which cyclization had occurred exclusively in the 1 position (entry 6). However, when an electron-withdrawing ester group was incorporated into the *para*-position of the aniline, only a 53% yield of quinoline **86** could be obtained employing 20 mol % of $Hg(OTf)_2$ (entry 7). The reaction was not as efficient when the distal end of the triple bond was substituted by either an alkyl or a vinylic group (entries 3, 8 and 9). However, we were able to efficiently cyclize substrates bearing electron-rich aromatic rings and either a butyl or cyclohexenyl group on the alkyne and the amount of catalyst could be reduced to 5 mol % in both cases (entries 8 and 9, Table 6). It is particularly noteworthy that a C-C double bond is readily accommodated in this later process.

Table 6. Synthesis of Quinolines by the $Hg(OTf)_2$-Catalyzed Cyclization of *N*-(2-Alkynyl)anilines in MeCN[a]

entry	substrate		$Hg(OTf)_2$ (mol %)	time (h)	product		% yield
							
1	R = Ph	**22**	10	6		**78**	96
2	R = *p*-$MeOC_6H_4$	**21**	10	6		**80**	88
3	R = *n*-Bu	**38**	15	12		**81**	50
4		**57**	10	6		**82**	79

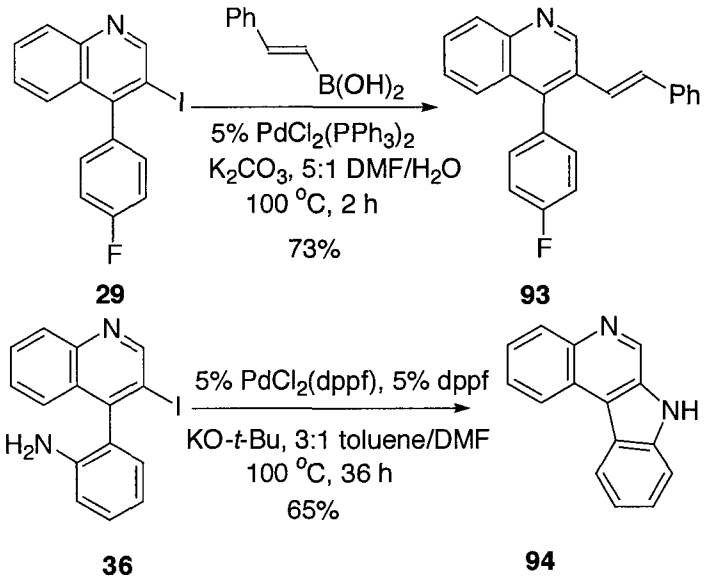
5		**59**	4	6		**83** + **84**	35 + 38
6		**63**	10	12		**85**	65
7		**50**	20	24		**86**	53
8		**87**	5	3		**88**	75
9		**89**	5	5		**90**	73
10		**45**	30	24		**91**	38

11		**75**	20	12		**92**	65

[a] To a solution of 0.3 mmol of the propargylic aniline in 3 mL of CH_3CN was added a catalytic amount of $Hg(OTf)_2$. The reaction mixture was stirred at room temperature for the indicated time.

These functionally-substituted quinolines, particularly the iodo derivatives, offer considerable potential for further elaboration. For example, iodoquinoline **29** undergoes a facile Suzuki reaction[26] with styrylboronic acid to afford the styryl-substituted quinoline **91** in a 73% yield (Scheme 5). Quinoline **91** is an analog of a CHMG-CoA reductase inhibitor.[3c] Iodoquinoline **36** readily undergoes an intramolecular palladium-catalyzed Buchwald-Hartwig amination[27] to produce the interesting tetracyclic diamine **92** in a 65% yield.

Scheme 5



Conclusions

A wide variety of 3-halogen-, selenium- and sulfur-containing quinolines have been readily synthesized under mild reaction conditions by the 6-*endo*-dig electrophilic cyclization of *N*-(2-alkynyl)anilines by ICl, I_2, Br_2, PhSeBr and ArSCl as electrophiles. The reaction affords quinolines in moderate to good yields and various functional groups are readily accommodated. Dihydroquinolines can be obtained when triflamides are used as the starting materials. Quinolium salts can be obtained when *N*-alkyl-*N*-(2-alkynyl)anilines are employed. Quinolines bearing a hydrogen in the 3 position have been synthesized by the $Hg(OTf)_2$-catalyzed ring closure of these same alkynylanilines. Finally, further conversion of the iodine moiety in these iodoquinolines to other functionally-substituted quinolines has been illustrated.

Experimental Section

General. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

Synthesis of Starting Materials. Compounds **1**, **3**, **5**, **7**, **9**, **11**, and **13** were prepared by the following general reaction. To a solution of *N*-phenyltrifluoromethanesulfonamide[28] (1.28 g, 5.0 mmol), PPh_3 (5.5 mmol) and the corresponding propargylic alcohol (5.5 mmol) in anhydrous THF (50 mL) at 0 °C was added DEAD (5.5 mmol). The resulting solution was

stirred at 0 °C for 1 h and an additional 3 h at room temperature. The mixture was washed with brine (50 mL) and the organic layer was dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on a silica gel column to afford the corresponding product.

***N*-Phenyl-*N*-(3-phenylprop-2-ynyl)trifluoromethanesulfonamide (1).** The indicated compound was prepared as a yellow oil from 3-phenyl-2-propyn-1-ol in a 90% yield as a sticky oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.75 (s, 2H), 7.31-7.36 (m, 5H), 7.44-7.47 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.56, 82.06, 86.97, 118.22, 122.08, 122.51, 128.61, 128.77, 129.15, 129.59, 129.83, 129.94, 131.91, 137.25 (extra peaks are due to F splitting); IR (CH_2Cl_2) 3067, 2978, 2927, 2251, 2221, 1595 cm^{-1}; HRMS *m/z* 339.0545 (calcd for $C_{16}H_{12}F_3NO_2S$, 339.0541).

***N*-[3-(3-Methoxyphenyl)prop-2-ynyl]-*N*-phenyltrifluoromethanesulfonamide (3).** The indicated compound was prepared from 3-(3-methoxyphenyl)-2-propyn-1-ol in a 90% yield as a yellow sticky oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 3H), 4.70 (s, 2H), 6.85-6.87 (m, 2H), 6.93-6.95 (m, 1H), 7.15-7.17 (m, 1H), 7.37-7.39 (m, 3H), 7.45-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.38, 55.23, 81.87, 86.80, 115.33, 116.90, 122.94, 123.57, 124.25, 129.46, 129.63, 129.66, 129.73, 129.87, 137.07, 159.47 (extra peaks due to F splitting); IR (CH_2Cl_2) 3071, 3012, 2967, 2945, 2837, 2251, 2222, 1598 cm^{-1}; HRMS *m/z* 369.0653 (calcd for $C_{17}H_{14}F_3NO_3S$, 369.0647).

***N*-Phenyl-*N*-[3-(4-methylphenyl)prop-2-ynyl]trifluoromethanesulfonamide (5).** The indicated compound was prepared from 3-(4-methylphenyl)-2-propyn-1-ol in a 95%

yield as a yellow sticky oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3 H), 4.74 (s, 2H), 7.13-7.18 (m, 2H), 7.25-7.40 (m, 3H), 7.44-7.60 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.09, 44.56, 82.06, 86.97, 118.22, 122.08, 122.51, 128.61, 129.15, 129.59, 129.83, 129.94, 131.91, 137.25 137.40 (extra peaks are due to F splitting); IR (CH_2Cl_2) 3067, 2978, 2927, 2251, 2221, 1595 cm^{-1}; HRMS *m/z* 353.0694 (calcd for $C_{17}H_{14}F_3NO_2S$, 353.0697).

***N*-[3-(4-Acetylphenyl)prop-2-ynyl]-*N*-phenyltrifluoromethanesulfonamide (7).** The indicated compound was prepared from 3-(4-acetylphenyl)-2-propyn-1-ol in an 88% yield as a yellow sticky oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.59 (s, 3H), 4.77 (s, 2H), 7.41-7.67 (m, 7H), 7.88-7.91 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.85, 44.50, 85.28, 86.10, 126.77, 128.47, 129.50, 129.91, 130.04, 132.05, 137.08, 137.17, 197.38; IR (CH_2Cl_2) 3067, 3008, 2982, 2927, 1691, 1602, 1398 cm^{-1}; HRMS *m/z* 381.0653 (calcd for $C_{18}H_{14}F_3NO_3S$, 381.0647).

***N*-Phenyl-*N*-[3-(4-methoxyphenyl)prop-2-ynyl)]trifluoromethanesulfonamide (9).** The indicated compound was prepared from 3-(4-methoxyphenyl)-2-propyn-1-ol in a 95% yield as a yellow sticky oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H), 4.74 (s, 2H), 6.83-6.86 (d, *J* = 9.0 Hz, 2H), 7.29-7.32 (d, *J* = 9.0 Hz, 2H), 7.44-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.70, 55.54, 80.72, 86.99, 114.14, 114.24, 118.23, 122.52, 123.96, 127.89, 129.61, 129.62, 129.78, 129.87, 129.92, 133.43, 137.29, 160.30; IR (CH_2Cl_2) 3071, 3012, 2967, 2945, 2837, 2251, 2222, 1598 cm^{-1}; HRMS *m/z* 369.0653 (calcd for $C_{17}H_{14}F_3NO_3S$, 369.0647).

***N*-Hept-2-ynyl-*N*-phenyltrifluoromethanesulfonamide (11).** The indicated compound was prepared from 2-heptyn-1-ol in a 78% yield as an yellow colorless oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86-0.88 (m, 3H), 1.27-1.42 (m, 4H), 2.10-2.14 (m, 2H), 4.48 (s, 2H), 7.37-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.45, 18.22, 21.76, 30.33, 44.06, 72.90, 87.79, 118.64, 121.85, 129.36, 129.46, 129.54, 137.09 (extra peaks due to F splitting); IR (CH_2Cl_2) 3071, 3045, 2960, 2938, 2875, 1595 cm^{-1}; HRMS *m/z* 319.0859 (calcd for $C_{14}H_{16}F_3NO_2S$, 319.0854).

***N*-(3-Cyclohex-1-en-1-yl-1-methylprop-2-ynyl)-*N*-phenyltrifluoromethanesulfonamide (13).** The indicated compound was prepared from 4-(1-cyclohexen-1-yl)-3-butyn-2-ol in a 70% yield as a yellow sticky oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38-1.40 (d, J = 6.8 Hz, 3H), 1.55-1.63 (m, 4H), 2.05-2.07 (m, 4H), 5.27-5.29 (m, 1H), 6.06 (s, 1H), 7.42 (s, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.41, 22.10, 22.17, 25.61, 28.81, 50.35, 83.71, 88.27, 118.58, 119.79, 121.79, 129.02, 129.92, 131.85, 133.26, 135.83 (extra peaks due to F splitting); IR (CH_2Cl_2) 2938, 2863, 2225, 1394 cm^{-1}; HRMS *m/z* 357.1016 (calcd for $C_{17}H_{18}F_3NO_2S$, 357.1010).

***N*-(3-Methoxyphenyl)-*N*-(3-phenylprop-2-ynyl)trifluoromethanesulfonamide (15).** The indicated compound was prepared from *N*-(3-methoxyphenyl)trifluoromethanesulfonamide and 3-phenyl-2-propyn-1-ol using the above standard Mitsunobu reaction conditions in an 85% yield as a yellowish oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 4.74 (s, 2H), 6.96-6.99 (m, 1H), 7.07-7.10 (m, 2H), 7.29-7.40 (m, 6H); ^{13}C NMR

($CDCl_3$, 75 Hz) δ 44.43, 55.41, 82.22, 86.86, 115.30, 115.51, 121.36, 121.99, 128.57, 129.11, 130.33, 131.78, 138.12, 160.45; IR (CH_2Cl_2) 2938, 2863, 2225, 1394 cm^{-1}; HRMS *m/z* 369.0653 (calcd for $C_{17}H_{14}F_3NO_3S$, 369.0647).

***N*-(4-Bromophenyl)-*N*-(3-phenylprop-2-ynyl)trifluoromethanesulfonamide (18).** The indicated compound was prepared from *N*-(4-bromophenyl)trifluoromethanesulfonamide and 3-phenyl-2-propyn-1-ol using the above standard Mitsunobu reaction conditions in a 70% yield as a colorless oil. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. ^1H NMR ($CDCl_3$, 300 MHz) δ 4.77 (s, 2H), 7.34-7.44 (m, 7H), 7.59-7.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 44.36, 81.71, 87.19, 121.76, 124.14, 128.59, 129.23, 131.09, 131.83, 132.99, 136.13; IR (CH_2Cl_2) 3064, 2975, 2927, 2856, 2251, 2222, 1483 cm^{-1}; HRMS *m/z* 418.9632 (calcd for $C_{16}H_{11}BrF_3NO_2S$, 418.9626).

Preparation of compound **20** can be found in our previous communication.[18]

General Procedure for the Electrophilic Cyclization of *N*-Triflamides by ICl. To a solution of *N*-phenyl-*N*-(3-phenylprop-2-ynyl)trifluoromethanesulfonamide (102 mg, 0.30 mmol) in CH_2Cl_2 (3.0 mL) at -78 °C was added ICl (58.5 mg, 0.36 mmol) in CH_2Cl_2 (0.5 mL) and the resulting solution was stirred at this temperature for 0.5 h. The reaction mixture was washed with satd aq $Na_2S_2O_3$ (20 mL) and the organic layer dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. To the crude solution of 3-iodo-1-trifluoromethanesulfonyl-4-phenyl-1,2-dihydroquinoline in MeOH (10 mL) was added NaOMe (3 mmol, 162 mg) and the mixture was stirred at r.t. in the presence of air for 12 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column.

Compounds **2**, **8**, **10**, **12** and **14** have been previously reported.[18]

3-Iodo-4-(3-methoxyphenyl)quinoline (4). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product as a white solid in 62% yield: 117-118 °C; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 3.84 (s, 3H), 6.78 (s, 1H), 6.81-6.83 (m, 1H), 7.03-7.06 (m, 1H), 7.41-7.50 (m, 3H), 7.68-7.72 (m, 1H), 8.08-8.10 (d, J = 6.6 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 55.43, 96.11, 114.26, 114.66, 121.40, 126.78, 127.43, 128.90, 129.48, 129.76, 129.86, 141.60, 147.17, 152.24, 156.65, 159.70; IR ($CHCl_3$) 2837, 1613, 1513, 1483, 1246 cm^{-1}; HRMS *m/z* 360.9972 (calcd for $C_{16}H_{12}INO$, 360.9964); Anal. Calcd for $C_{16}H_{12}INO$: C, 53.1; H, 3.3; N 3.9; Found: C, 53.1; H, 3.9; N, 3.5.

3-Iodo-4-(4-methylphenyl)quinoline (6). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford a 45% yield of the product as a white solid: mp 155-156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (s, 3H), 7.15-7.17 (d, J = 8.0 Hz, 2H), 7.26-7.43 (m, 3H), 7.49-7.51 (d, J = 8.4 Hz, 2H), 7.69-7.73 (m, 1H), 8.10-8.12 (d, J = 8.4 Hz, 1H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.52, 96.60, 126.85, 127.32, 128.99, 129.17, 129.36, 129.49, 129.68, 137.41, 138.57, 147.24, 152.53, 156.66; IR ($CHCl_3$) 2900, 2852, 1566, 1494 cm^{-1}; HRMS *m/z* 345.0018 (calcd for $C_{16}H_{12}IN$, 345.0015).

3-Iodo-7-methoxy-4-phenylquinoline (16). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product as a white solid: mp 142-143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (s, 3H), 7.03-7.07 (m, 1H), 7.23-7.27 (m, 2H), 7.33-7.36 (d, J = 9.3 Hz, 1H), 7.42-7.43 (d, J = 2.7 Hz, 1H), 7.51-7.54 (m, 3H), 9.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.83, 107.57, 120.56, 124.42, 128.14, 128.80, 128.81, 129.28, 140.62, 149.25, 152.24, 157.06, 161.01; IR ($CHCl_3$) 2837, 1613, 1513, 1483, 1246 cm^{-1}; HRMS *m/z* 360.9972 (calcd for $C_{16}H_{12}INO$, 360.9964).

3-Iodo-5-methoxy-4-phenylquinoline (17). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product as a white solid: mp 134-135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.39 (s, 3H), 6.79-6.81 (d, J = 7.6 Hz, 4H), 7.10-7.13 (m, 1H), 7.26-7.46 (m, 3H), 7.61-7.65 (t, J = 7.6 Hz, 1H), 7.72-7.74 (m, 1H), 9.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.76, 98.78, 106.95, 120.94, 122.26, 127.13, 127.54, 129.97, 145.80, 149.06, 150.78, 155.57, 156.83; IR ($CHCl_3$) 2837, 1613, 1513, 1483, 1246 cm^{-1}; HRMS *m/z* 360.9972 (calcd for $C_{16}H_{12}INO$, 360.9964).

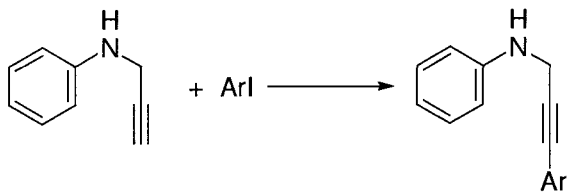
6-Bromo-3-iodo-4-phenylquinoline (19). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford the product as a white solid: mp 185-186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.24 (m, 2H), 7.54-7.58 (m, 4H), 7.75-7.77 (m, 1H), 7.95-7.97 (d, J = 8.8 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 97.56, 121.69, 128.81, 128.92, 129.00, 129.05, 129.93, 131.29, 133.32, 139.66, 145.84, 151.53, 157.08; IR ($CHCl_3$) 2919, 2845, 1483 cm^{-1}; HRMS *m/z* 408.8967 (calcd for $C_{15}H_9BrIN$, 408.8963).

Electrophilic Cyclization of *N*-(2-Alkynyl)anilines (Table 3).

Synthesis of Starting Materials.

Compounds **21**, **22**, **28**, **30**, **35**, **45**, **50**, **60** and **63** have been previously reported.[18]

Compounds **31** and **33** were prepared by the Sonogashira reaction of *N*-(2-propynyl)aniline with the corresponding aryl halide. A typical reaction follows.



To a solution of Et_3N (30 mL), $PdCl_2(PPh_3)_2$ (2 mol %), 3.0 mmol of *N*-(2-propynyl)aniline, and 1.2 equiv of aryl iodide (stirring for 3 min beforehand) was added CuI (1 mol %). The reaction mixture was flushed with Ar and the flask was then sealed. The mixture was stirred at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was filtered, washed with a satd aq NaCl solution, and extracted with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel.

***N*-[3-(4-Nitrophenyl)prop-2-ynyl]aniline (31).** The indicated compound was prepared as a pale yellow sticky oil from 4-iodonitrobezene in an 80% yield. The reaction mixture was chromatographed using 4:1 hexane/EtOAc: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06 (s, 1H), 4.14 (s, 2H), 6.70-6.82 (m, 3H), 7.19-7.25 (m, 2H), 7.41-7.45 (m, 2H), 8.05-8.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.67, 81.70, 92.69, 113.86, 118.95, 123.75, 129.58, 130.10, 132.69, 147.14, 147.23; IR (CH_2Cl_2) 3350 cm^{-1}; HRMS *m/z* 252.0895 (calcd for $C_{15}H_{12}N_2O_2$, 252.0899).

***N*-(3-Pyridin-3-ylprop-2-ynyl)aniline (33).** The indicated compound was prepared as a pale yellow sticky oil from 3-bromopyridine in an 80% yield. The reaction mixture was chromatographed using 1:1 hexane/EtOAc: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60-3.80 (br s, 1H), 4.17 (s, 2H), 6.73-6.83 (m, 3H), 7.18-7.27 (m, 3H), 7.64-7.68 (m, 1H), 8.49-8.52 (m, 1H), 8.63-8.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.68, 80.17, 90.33, 113.82, 118.87, 120.31, 123.21, 129.53, 138.92, 147.18, 148.78, 152.60; IR (CH_2Cl_2) 3400 cm^{-1}; HRMS *m/z* 208.0998 (calcd for $C_{14}H_{12}N_2$, 208.1000).

Compounds **38**, **39**, **41**, **43**, **46**, **48**, **53**, **55**, **59** and **65** were prepared by reaction of the appropriate aniline (2 equiv) and the corresponding propargylic mesylate at room temperature in CH_3CN.[29]

***N*-(2-Heptynyl)aniline (38).** To a solution of the methanesulfonate[30] of 2-heptyn-1-ol (950 mg, 5.0 mmol) in 50 mL of CH_3CN was added aniline (930 mg, 10 mmol). After being stirred for 20 h under N_2, the reaction was quenched by adding brine. The reaction mixture was extracted with Et_2O (2 × 30 mL). The extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford 589 mg of the product (63% yield) as a light yellow oil. The spectral properties were identical with those previously reported.[31]

***N*-(3-Trimethylsilylprop-2-ynyl)aniline (39).** Using the same procedure used to prepare aniline **38**, aniline and 3-bromo-1-trimethylsilyl-1-propyne were employed to afford the indicated compound in a 42% yield as a colorless oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (br s, 1H), 3.95 (s, 2H), 6.67-6.71 (m, 2H), 6.77-6.82 (m, 1H), 7.20-7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0, 34.84, 88.13, 103.25, 113.55, 118.43, 129.22, 147.19; IR (CH_2Cl_2) 3342 cm^{-1}; HRMS *m/z* 203.1127 (calcd for $C_{12}H_{17}NSi$, 203.1130).

***N*-Propargylaniline (41).** Using the procedure used to prepare aniline **38**, aniline and the methanesulfonate of propargyl alcohol were employed to afford the indicated compound in a 50% yield as a colorless oil. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. The spectral properties for this compound were similar to those previously reported.[32]

***N*-(4,4,1-Trimethylpent-2-ynyl)aniline (43).** Using the procedure used to prepare aniline **38**, aniline and the methanesulfonate of 5,5-dimethyl-3-hexyn-2-ol were employed to afford the indicated compound in a 35% yield as a colorless oil. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 9H), 1.49-1.51 (d, J = 6.9 Hz, 3H), 3.70 (br s, 1H), 4.20-4.27 (q, J = 6.9 Hz, 1H), 6.72-6.81 (m, 3H), 7.20-7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.03, 27.47, 31.33, 41.46, 80.28, 91.23, 114.36, 118.25, 129.23, 147.16; IR (CH_2Cl_2) 3360 cm^{-1}; HRMS *m/z* 187.1354 (calcd for $C_{13}H_{17}N$, 187.1361).

***N*-(1-Benzyl-3-phenylprop-2-ynyl)aniline (46).** Using the same procedure used to prepare aniline **38**, aniline and the methanesulfonate of 1,4-diphenyl-3-butyn-2-ol were employed to afford the indicated compound in a 51% yield as a sticky yellow oil. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.13-3.17 (m, 2H), 3.84 (br s, 1H), 4.56-4.61 (m, J = 6.3 Hz, 1H), 6.71-6.78 (m, 3H), 7.17-7.36 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.82, 47.72, 84.44, 89.72, 114.52, 118.81, 123.24, 127.26, 128.45, 128.51, 128.70, 129.54, 130.13, 131.94, 137.20, 146.69; IR (CH_2Cl_2) 3401, 3056, 3030, 2927, 2856, 1602, 1502 cm^{-1}; HRMS *m/z* 297.1523 (calcd for $C_{22}H_{19}N$, 297.1518).

***N*-(3-Phenylprop-2-ynyl)-4-bromoaniline (48).** Using the same procedure used to prepare aniline **38**, 4-bromoaniline and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound in a 60% yield as a white solid. The reaction mixture was chromatographed using 10:1 hexane/EtOAc: mp 92-93 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.99 (br s, 1H), 4.11 (s, 2H), 6.59-6.63 (m, 2H), 7.25-7.33 (m, 5H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.72, 83.76, 85.98, 110.47, 115.39, 122.89, 128.52,

128.58, 131.93, 132.18, 146.31; IR (CH_2Cl_2) 3297, 3075, 3034, 2912, 2860, 1591, 1502, 1491 cm^{-1}; HRMS *m/z* 285.0157 (calcd for $C_{15}H_{12}BrN$, 285.0153).

***N*-(3-Phenylprop-2-ynyl)-4-nitroaniline (53).** This compound was synthesized by using the following procedure. A mixture of 4-nitroaniline (7.19 mmol) and anhydrous K_2CO_3 (21.6 mmol) in dry DMF (15 mL) was heated to 55-60 °C for half an hour under an inert atmosphere. The mixture was then cooled to room temperature and phenylpropargyl bromide (8.62 mmol) was added through a septum using a syringe. The mixture was stirred for 5 h at 60 °C and poured into ice water with stirring. Stirring was continued for 10 min and the sticky solid, which separated, was filtered off to afford the crude product. The reaction mixture was chromatographed using 3:1 hexane/EtOAc and desired compound **53** was afforded in a 20% yield as an orange oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.24-4.26 (d, *J* = 6.0 Hz, 2H), 4.83 (br s, 1H), 6.67-6.70 (d, *J* = 6.9 Hz, 2H), 7.26-7.33 (m, 3H), 7.39-7.41 (m, 2H), 8.13-8.15 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.01, 84.21, 84.26, 111.90, 122.26, 126.28, 128.42, 128.71, 131.77, 139.02, 152.23; IR ($CHCl_3$) 3060, 1686, 1622, 1528, 1348 cm^{-1}; HRMS *m/z* 252.0902 (calcd for $C_{15}H_{12}N_2O_2$, 252.0899).

***N*-(3-Phenylprop-2-ynyl)-4-methoxyaniline (55).** Using the same procedure used to prepare aniline **38**, 4-methoxyaniline and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound. The residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford the product in a 55% yield as a sticky yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.70-3.80 (br s, 1H), 3.79 (s, 3H), 4.13 (s, 2H), 6.74-6.77 (d, *J* = 8.7 Hz, 2H), 6.87-6.90 (d, *J* = 8.7 Hz, 2H), 7.32-7.34 (m, 3H), 7.45-7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.76, 55.98, 83.56, 87.22, 115.10, 115.47,

123.28, 128.49, 128.58, 132.00, 141.58, 153.16; IR (CH_2Cl_2) 3398, 2929, 2833, 1603, 1504 cm^{-1}; HRMS *m/z* 237.1158 (calcd for $C_{16}H_{15}NO$, 237.1154).

***N*-(3-Phenylprop-2-ynyl)-3,5-dimethylaniline (57).** Using the same procedure used to prepare aniline **38**, 3,5-dimethylaniline and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound in a 48% yield as a light orange oil. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 6H), 3.70-3.85 (br s, 1H), 4.04 (s, 2H), 6.30 (s, 2H), 6.42 (s, 1H), 7.22-7.24 (m, 3H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.93, 34.94, 83.59, 87.20, 111.90, 120.81, 123.42, 128.56, 128.66, 132.11, 139.19, 147.68; IR (CH_2Cl_2) 3398, 2929, 1603, 1504 cm^{-1}; HRMS *m/z* 235.1364 (calcd for $C_{17}H_{17}N$, 235.1361).

***N*-(3-Phenylprop-2-ynyl)-3-methoxyaniline (59).** Using the procedure used to prepare aniline **38**, 3-methoxyaniline and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound in a 51% yield as a yellow oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 4.17 (br s, 3H), 6.39-6.47 (m, 3H), 7.19-7.25 (t, J = 8.1 Hz, 6H), 7.35-7.37 (m, 3H), 7.50-7.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.7, 56.0, 81.0, 86.8, 97.9, 102.5, 104.6, 122.3, 128.1, 128.2, 130.3, 132.1, 144.5, 162.8; IR (CH_2Cl_2) 3398, 2929 cm^{-1}; HRMS *m/z* 237.1158 (calcd for $C_{16}H_{15}NO$, 237.1154).

***N*-(3-Phenylprop-2-ynyl)-3-aminopyridine (65).** Using the procedure used to prepare aniline **38**, 3-aminopyridine and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound in a 30% yield as a light red oil. The reaction mixture was chromatographed using 3:1 $CHCl_3$/MeOH. ^1H NMR (CD_3OD, 400 MHz) δ 5.63 (s, 2H), 7.34-7.40 (m, 3H), 7.50-7.52 (m, 2H), 7.68-7.69 (m, 2H), 8.20 (s, 1H),

8.35 (s, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 50.57, 79.12, 89.52, 120.95, 127.58, 127.93, 128.15, 128.39, 129.46, 130.56, 131.73, 149.41; IR (CH_2Cl_2) 3401, 1507; HRMS *m/z* 208.0998 (calcd for $C_{16}H_{15}NO$, 208.1000).

***N*-(3-Phenylprop-2-ynyl)-2-methylbenzene-1,3-diamine (69).** The reaction mixture was chromatographed using 1:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90 (s, 3H), 3.59 (s, 3H), 4.11 (s, 2H), 6.19-6.22 (d, *J* = 9.0 Hz, 1H), 6.26-6.29 (d, *J* = 8.1 Hz, 1H), 6.93-6.98 (m, 1H), 7.24-7.26 (m, 3H), 7.39-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.35, 35.28, 83.54, 87.30, 103.02, 107.41, 107.58, 123.30, 127.24, 128.54, 128.61, 132.07, 145.13, 146.19; IR (CH_2Cl_2) 3401; HRMS *m/z* 236.1309 (calcd for $C_{16}H_{16}N_2$, 236.1313).

6-Methoxy-1-(3-phenylprop-2-ynyl)-3,4-dihydroquinolin-2(1*H*)-one (71). Using the procedure used to prepare aniline **38**, 6-methoxy-3,4-dihydroquinolin-2-one[33] and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound in a 70% yield as a sticky oil. The reaction mixture was chromatographed using 3:1 hexane/EtOAc. ^{1}H NMR (CD_3Cl, 300 MHz) δ 2.64-2.69 (t, *J* = 7.8 Hz, 2H), 2.85-2.90 (t, *J* = 7.8 Hz, 2H), 3.78 (s, 3H), 4.88 (s, 2H), 6.74-6.83 (m, 2H), 7.22-7.26 (m, 4H), 7.37-7.39 (m, 2H); ^{13}C NMR (CD_3Cl, 75 MHz) δ 25.84, 31.94, 33.04, 55.77, 83.62, 84.62, 112.16, 114.18, 116.46, 122.88, 127.98, 128.43, 128.58, 132.05, 133.02, 155.73, 169.65; IR ($CHCl_3$) 3060, 2960, 2837, 2365, 2340, 1673, 1506 cm^{-1}; HRMS *m/z* 291.1263 (calcd for $C_{19}H_{17}NO_2$, 291.1259).

***N*,*N*-Di(3-phenylprop-2-ynyl)-4-methoxyaniline (73).** Using the same procedure used to prepare aniline **38**, 4-methoxyaniline and the methanesulfonate of 3-phenyl-2-propyn-1-ol were employed to afford the indicated compound. The residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford the product in a 45% yield

as a sticky yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (s, 3H), 4.44 (s, 4H), 6.99-7.02 (d, J = 9.0 Hz, 2H), 7.19-7.22 (d, J = 9.0 Hz, 2H), 7.34-7.36 (m, 6H), 7.52-7.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.90, 55.76, 85.31, 85.70, 114.79, 119.54, 123.43, 128.55, 128.64, 132.16, 142.95, 154.52; IR (CH_2Cl_2) 3056, 2997, 2934, 2834, 1517, 1491, 1246 cm^{-1}; HRMS m/z 351.1630 (calcd for $C_{25}H_{21}NO$, 351.1623).

***N*-[3-(2-Bromophenyl)prop-2-ynyl]-2-methoxy-5-nitroaniline (75).** Using the same procedure used to prepare aniline **38**, 2-methoxy-5-nitroaniline and 3-(2-bromophenyl)propargyl bromide were employed to afford the indicated compound. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95 (s, 3H), 4.30-4.31 (d, J = 5.6 Hz, 2H), 4.81 (s, 1H), 6.78-6.80 (d, J = 8.8 Hz, 1H), 7.12-7.16 (t, J = 8.0 Hz, 1H), 7.20-7.24 (t, J = 7.6 Hz, 1H), 7.41-7.44 (dd, J = 8.8, 1.6 Hz, 1H), 7.53-7.55 (d, J = 8.0 Hz, 1H), 7.65-7.66 (d, J = 2.8 Hz, 1H), 7.70-7.72 (dd, J = 8.8, 2.8 Hz, 1H); ^{13}C NMR (CD_3Cl, 100 MHz) δ 33.96, 56.15, 82.42, 89.85, 105.32, 108.23, 114.48, 124.75, 125.67, 127.02, 129.65, 132.42, 133.65, 137.16, 142.37, 152.08; IR (CH_2Cl_2) 3356, 2934, 2837, 1491 cm^{-1}; HRMS m/z 360.0106 (calcd for $C_{16}H_{13}BrN_2O_3$, 360.0110).

General Procedure for the Electrophilic Cyclization of *N*-(2-Alkynyl)anilines by I_2. 0.3 Mmol of the propargylic aniline, 3 equiv of I_2, 2 equiv of $NaHCO_3$, and 3 mL of CH_3CN were placed in a vial. The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC to establish completion. When finely ground iodine powder was employed, all reactions were complete in 0.5 h. The reaction mixture was then diluted with 25 mL of ether and washed with 20 mL of satd aq $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined

organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

General Procedure for the Electrophilic Cyclization of *N*-(2-Alkynyl)anilines by ICl , Br_2, PhSeBr or *p*-$O_2NC_6H_4SCl$. 0.3 Mmol of the propargylic aniline, 2 equiv of $NaHCO_3$ and 2 mL of CH_3CN were placed in a vial. 2 Equiv of ICl, Br_2, PhSeBr or *p*-$O_2NC_6H_4SCl$ in 1 mL of CH_3CN were added dropwise to the vial. The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was then diluted with 25 mL of ether, and washed with 20 mL of satd aq $Na_2S_2O_3$ (for the reactions of ICl and Br_2) or satd aq NaCl (for the reactions of PhSeBr and *p*-$O_2NC_6H_4SCl$). The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds **29**, **36**, **61**, **62** and **64** have been previously reported.[18]

4-(4-Methoxyphenyl)-3-(phenylseleno)quinoline (25). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 86 mg (74%) of the product as a yellow solid: mp 93-94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.91 (s, 3H), 7.06 (d, J = 6.0 Hz, 2H), 7.26-7.32 (m, 5H), 7.43-7.57 (m, 3H), 7.63-7.68 (m, 1H), 7.68-7.73 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.57, 114.25, 126.23, 127.22, 127.34, 128.44, 128.47, 129.16, 129.61, 129.70, 129.74, 129.85, 130.87, 134.81, 147.08, 148.27, 152.43, 159.99; IR ($CHCl_3$) 2923, 2851, 1736, 1250 cm^{-1}; HRMS *m/z* 391.0482 (calcd for $C_{22}H_{17}NOSe$, 391.0475).

3,6-Dibromo-4-(4-methoxyphenyl)quinoline (26). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford a 51% yield of the product as a light

yellow wax: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (s, 3H), 7.06-7.08 (d, J = 8.8 Hz, 2H), 7.21-7.24 (m, 3H), 7.67 (d, J = 2.0 Hz, 1H), 7.74-7.77 (m, 1H), 7.95-7.97 (d, J = 9.2 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.0, 113.3, 114.6, 120.9, 121.9, 127.9, 128.3, 130.4, 132.5, 148.8, 149.9, 153.7, 162.5; IR ($CHCl_3$) 2925 cm^{-1}; HRMS *m/z* 390.9201 (calcd for $C_{16}H_{11}Br_2NO$, 390.9207).

4-(4-Methoxyphenyl)-3-(4-nitrophenylthio)quinoline (27). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 14 mg (12%) of the product as a yellow sticky oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (s, 3H), 6.95-6.97 (d, J = 8.0 Hz, 2H), 7.14-7.20 (m, 4H), 7.28-7.30 (d, J = 8.4 Hz, 1H), 7.75-7.77 (d, J = 8.8 Hz, 1H), 8.05-8.11 (m, 4H), 8.22-8.24 (d, J = 8.4 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.40, 114.11, 124.30, 124.32, 126.54, 128.29, 128.67, 128.90, 130.62, 130.95, 131.07, 134.38, 145.75, 146.11, 146.20, 152.33, 160.26 ; IR ($CHCl_3$) 3058, 2930, 1576, 1441, 1352 cm^{-1}; HRMS *m/z* 388.0880 (calcd for $C_{22}H_{16}N_2O_3S$, 388.0882).

2-Benzyl-3-iodo-4-phenylquinoline (47). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 48 mg (38%) of quinoline **47** as a white solid: mp 117-118 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.73 (s, 2 H), 7.19-7.41 (m, 10H), 7.51-7.55 (m, 2H), 7.68-7.73 (m, 1H), 8.10-8.13 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.83, 100.55, 126.53, 127.04, 127.29, 128.53, 128.64, 128.79, 129.24, 129.30, 129.52, 130.06, 138.61, 142.31, 147.16, 154.78, 161.01 (one carbon was missing due to overlap); IR ($CHCl_3$) 3060, 3030, 2923, 2850, 1567, 1483 cm^{-1}; HRMS *m/z* 421.0336 (calcd for $C_{22}H_{16}IN$, 421.0328).

6-Bromo-4-phenyl-3-(phenylseleno)quinoline (49). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 99 mg (75%) of quinoline **49** as a light

yellow solid: mp 127-128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.33 (m, 5H), 7.48-7.60 (m, 5H), 7.60 (s, 1H), 7.68-7.71 (m, 1H), 7.89-7.91 (d, J = 8.8 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 121.39, 127.93, 128.49, 128.66, 128.68, 128.97, 129.01, 129.04, 129.27, 129.84, 131.31, 132.44, 135.16, 136.48, 145.31, 146.68, 152.06; IR ($CHCl_3$) 3058, 1600, 1576, 1481, 1441 cm^{-1}; HRMS *m/z* 432.9540 (calcd for $C_{21}H_{14}BrNSe$, 432.9534).

Ethyl 3-iodo-4-phenylquinoline-6-carboxylate (51). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 106 mg (88%) of the product as a yellow solid: mp 150-151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.36 (t, J = 7.2 Hz, 3H), 4.32-4.37 (q, J = 7.2 Hz, 2H), 7.26-7.29 (m, 2H), 7.56-7.28 (m, 3H), 8.14 (d, J = 8.8 Hz, 1H), 8.22 (m, 1H), 8.28-8.31 (m, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.28, 61.46, 97.28, 128.22, 128.83, 129.08, 129.23, 129.26, 129.71, 129.84, 139.61, 148.97, 153.67, 158.64, 165.82; IR ($CHCl_3$) 2974, 1724 cm^{-1}; HRMS *m/z* 403.0075 (calcd for $C_{18}H_{14}INO_2$, 403.0069).

Ethyl 4-phenyl-3-(phenylseleno)quinoline-6-carboxylate (52). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 67 mg (56%) of the product as a yellow solid: mp 125-127 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.37 (m, J = 7.2 Hz, 3H), 4.32-4.36 (m, J = 7.2 Hz, 2H), 7.26-7.36 (m, 5H), 7.50-7.57 (m, 5H), 8.08-8.10 (m, 1H), 8.22-8.26 (m, 2H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.29, 61.36, 127.22, 128.23, 128.46, 128.63, 128.78, 128.87, 128.95, 129.01, 129.04, 129.34, 129.82, 135.07, 136.48, 148.50, 149.01, 153.81, 166.14 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$) 2974, 1721 cm^{-1}; HRMS *m/z* 433.0589 (calcd for $C_{24}H_{19}NOSe$, 433.0581); Anal. Calcd for $C_{24}H_{19}NOSe$: C, 66.5; H, 4.4; N 3.2; Found: C, 65.8; H, 4.8; N, 3.1.

3-Iodo-6-nitro-4-phenylquinoline (54). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 89 mg of product (79%) as a light yellow solid: mp 195-196 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26-7.30 (m, 2H), 7.61-7.62 (m, 3H), 8.24-8.27 (d, *J* = 9.2 Hz, 1H), 8.41 (s, 1H), 8.45-8.48 (m, 1H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 98.58, 123.20, 123.59, 127.95, 128.93, 129.16, 129.61, 131.56, 138.82, 146.12, 149.21, 154.35, 160.11; IR ($CHCl_3$) 2930, 1544, 1352 cm^{-1}; HRMS *m/z* 375.9715 (calcd for $C_{15}H_9IN_2O_2$, 375.9709).

3-Iodo-6-methoxy-4-phenylquinoline (56). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product as a white solid in a 75% yield: mp 153-154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H), 6.69-6.68 (d, *J* = 2.4 Hz, 1H), 7.26-7.28 (m, 2H), 7.34-7.37 (m, 1H), 7.52-7.58 (m, 3H), 7.99-8.01 (d, *J* = 9.2 Hz, 1H), 9.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.42, 97.01, 104.80, 122.08, 128.67, 128.79, 129.00, 130.99, 140.67, 143.42, 150.85, 154.17, 158.30; IR ($CHCl_3$) 2837, 1613, 1513, 1483, 1246 cm^{-1}; HRMS *m/z* 360.9972 (calcd for $C_{16}H_{12}INO$, 360.9964).

3-Iodo-5,7-dimethyl-4-phenylquinoline (58). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product as a white solid in a 72% yield: mp 79-80 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 3H), 2.47 (s, 3H), 7.12 (s, 1H), 7.17-7.20 (m, 2H), 7.46-7.50 (m, 3H), 7.78 (s, 1H), 9.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.64, 24.92, 98.85, 126.30, 128.04, 128.50, 128.59, 129.30, 133.17, 135.32, 139.84, 145.35, 149.22, 151.89, 155.99; IR ($CHCl_3$) 3056, 3023, 2971, 2927, 2863, 1624, 1443 cm^{-1}; HRMS *m/z* 359.0171 (calcd for $C_{17}H_{14}IN$, 359.0171).

7-Amino-3-iodo-8-methyl-4-phenylquinoline (70). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 38 mg (35%) as a white wax: ^{1}H NMR

($CDCl_3$, 300 MHz) δ 2.52 (s, 3H), 3.99 (br s, 2H), 6.75-6.78 (d, J = 9.0 Hz, 1H), 7.05-7.08 (d, J = 9.0 Hz, 1H), 7.13-7.18 (m, 3H), 7.41-7.46 (m, 3H), 9.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.67, 91.66, 115.16, 119.05, 123.54, 125.45, 128.56, 128.67, 129.35, 141.19, 145.31, 147.28, 152.32, 155.68; IR ($CHCl_3$) 3056, 3023, 2971, 2927, 2863, 1624, 1443 cm^{-1}; HRMS *m/z* 359.0171 (calcd for $C_{17}H_{14}IN$, 359.0171).

6-Iodo-9-methoxy-3-oxo-7-phenyl-2,3-dihydro-1*H*-pyrido[3,2,1-*ij*]quinolinium chloride (72). The reaction mixture was chromatographed using EtOAc to afford 67.7 mg (50%) of a yellow solid: mp 175-176 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.86-2.90 (t, J = 7.6 Hz, 2H), 3.49-3.52 (t, J = 7.6 Hz, 2H), 3.63 (s, 3H), 6.55-6.56 (d, J = 2.4 Hz, 1H), 7.22-7.24 (m, 3H), 7.51-7.54 (m, 3H), 9.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.43, 35.10, 55.33, 97.03, 103.62, 122.26, 128.72, 128.81, 128.90, 130.72, 140.75, 140.85, 141.35, 151.86, 152.81, 157.93, 177.50; IR ($CHCl_3$) 2960, 2837, 1713 cm^{-1}.

3-Iodo-6-methoxy-4-phenyl-1-(3-phenylprop-2-ynyl)quinolinium iodide (74). The reaction mixture was chromatographed using EtOAc to afford 112 mg (62%) of a deep brown solid: mp 151-152 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.66 (s, 3H), 6.07 (s, 2H), 7.00 (s, 1H), 7.30-7.64 (m, 10H), 7.85-7.89 (m, 1H), 8.43-8.46 (d, J = 7.2 Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (d_6-acetone, 100 MHz) δ 49.19, 55.95, 79.79, 90.27, 93.75, 107.89, 120.98, 121.35, 127.74, 128.41, 128.81, 129.37, 129.87, 130.34, 131.92, 132.02, 133.23, 138.50, 151.97, 152.01, 160.74, 162.57; IR ($CHCl_3$) 2945 cm^{-1}.

4-(2-Bromophenyl)-3-iodo-8-methoxy-5-nitroquinoline (76). The reaction mixture was chromatographed using 2:1 hexane/EtOAc to afford **76** as a white wax in 80% yield: ^1H NMR ($CDCl_3$, 400 MHz) δ 4.18 (s, 3H), 7.05-7.07 (d, J = 8.4 Hz, 1H), 7.11-7.14 (dd, J = 7.2, 1.6 Hz, 1H), 7.33-7.43 (m, 2H), 7.66-7.68 (dd, J = 8.0, 1.2 Hz, 1H), 7.71-7.73 (d, J = 8.4 Hz,

1H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.97, 104.00, 105.96, 121.36, 123.53, 125.29, 127.42, 130.97, 133.06, 139.21, 140.16, 140.88, 147.89, 157.23, 158.60; IR ($CHCl_3$) 2927, 2863, 1626, 1447 cm^{-1}; HRMS *m/z* 483.8917 (calcd for $C_{16}H_{10}BrIN_2O_3$, 483.8920).

Hg(OTf)$_2$-Catalyzed Cyclization of *N*-(2-Alkynyl)anilines (Table 6).

Preparation of the *N*-(2-alkynyl)anilines.

***N*-(Hept-2-ynyl)-3,5-dimethoxyaniline (87).** Using the procedure used to prepare aniline **38**, 3,5-dimethoxyaniline and the methanesulfonate of 2-heptyn-1-ol were employed to afford the indicated compound in a 49% yield as an colorless oil. The reaction mixture was chromatographed using 15:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87-0.91 (t, *J* = 7.2 Hz, 1H), 1.35-1.48 (m, 4H), 2.15-2.18 (m, 2H), 3.74 (s, 6H), 3.84 (s, 2H), 3.85 (br s, 1H), 5.84-5.85 (d, *J* = 2.4 Hz, 2H), 5.91-5.92 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.63, 18.43, 21.97, 30.83, 34.20, 55.19, 83.92, 90.58, 92.26, 149.40, 161.67; IR ($CHCl_3$) 3394, 2960, 2938, 2871, 1617 cm^{-1}; HRMS *m/z* 247.1576 (calcd for $C_{15}H_{21}NO_2$, 247.1572).

***N*-(3-Cyclohex-1-en-1-ylprop-2-ynyl)-3,5-dimethoxyaniline (89).** Using the procedure used to prepare aniline **38**, 3,5-dimethoxyaniline and the methanesulfonate of 4-(1-cyclohexen-1-yl)-3-butyn-2-ol were employed to afford the indicated compound in a 43% yield as a colorless oil. The reaction mixture was chromatographed using 15:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54-1.62 (m, 4H), 2.05-2.08 (m, 4H), 3.74 (s, 6H), 3.98 (s, 2H), 5.84-5.85 (d, *J* = 2.4 Hz, 2H), 5.91-5.92 (t, *J* = 2.4 Hz, 1H), 6.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.53, 22.32, 25.64, 29.26, 34.54, 55.21, 83.37, 85.27, 90.64, 92.25, 120.33, 135.03, 149.31, 161.66; IR ($CHCl_3$) 3398, 3001, 2938, 2852, 1610 cm^{-1}; HRMS *m/z* 271.1576 (calcd for $C_{17}H_{21}NO_2$, 271.1572).

General Procedure for the $Hg(OTf)_2$-Catalyzed Cyclization of *N*-(2-Alkynyl)anilines. To a vial containing a solution of 0.3 mmol of the propargylic aniline in 3 mL of CH_3CN was added a catalytic amount of $Hg(OTf)_2$. The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC to establish completion. The reaction mixture was then diluted with 25 mL of ether, and washed with 20 mL of satd aq NaI. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers was washed further with 25 mL of satd aq NaCl. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

The spectra for 4-phenylquinoline (**78**)[34] and 4-*n*-butylquinoline (**81**)[35] have been previously reported.

4-(4-Methoxyphenyl)quinoline (80). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 62 mg of the product (88%) as a light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.91 (s, 3H), 7.05-7.08 (d, J = 8.7 Hz, 2H), 7.32-7.33 (d, J = 4.2 Hz, 2H), 7.44-7.53 (m, 3H), 7.70-7.75 (m, 1H), 7.96-7.99 (d, J = 8.4 Hz, 1H), 8.15-8.18 (d, J = 8.4 Hz, 1H), 8.92-8.93 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.46, 114.11, 121.34, 125.97, 126.54, 127.00, 129.30, 129.89, 130.33, 130.86, 148.26, 148.80, 150.06, 159.91; IR ($CHCl_3$) 3060, 2930, 2849, 1617 cm^{-1}; HRMS *m/z* 235.1001 (calcd for $C_{16}H_{13}NO$, 235.0997).

5,7-Dimethyl-4-phenylquinoline (82). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 55 mg of the product (79%) as a light yellow solid: mp 87-88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 3H), 2.51 (s, 3H), 7.12-7.13 (d, J = 4.0 Hz, 2H), 7.30-7.32 (m, 2H), 7.42-7.43 (m, 3H), 7.83 (s, 1H), 8.80-8.81 (d, J = 4.0 Hz, 1H), 8.15-

8.18 (d, J = 8.4 Hz, 1H), 8.92-8.93 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.47, 24.39, 122.78, 124.35, 127.71, 127.74, 127.90, 128.78, 132.22, 135.26, 139.00, 142.59, 148.66, 148.76, 150.13; IR ($CHCl_3$) 3056, 3030, 2971, 2927, 1621, 1576 cm^{-1}; HRMS *m/z* 233.1208 (calcd for $C_{17}H_{15}N$, 233.1205).

7-Methoxy-4-phenylquinoline (83) and 5-methoxy-4-phenylquinoline (84). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 25 mg of the product **83** (35%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3H), 7.14-7.17 (m, 1H), 7.20-7.21 (d, J = 4.4 Hz, 1H), 7.48-7.52 (m, 6H), 7.90-7.82 (d, J = 9.2 Hz, 1H), 8.85-8.86 (d, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.59, 107.67, 119.49, 121.88, 127.06, 128.43, 128.60, 129.53, 138.22, 148.42, 150.25, 150.52, 160.52; IR ($CHCl_3$) 3064, 2938, 2834, 1621 cm^{-1}; HRMS *m/z* 235.1001 (calcd for $C_{16}H_{13}NO$, 235.0997). The product **84** was also obtained (27 mg, 38%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.52 (s, 3H), 6.82-6.84 (d, J = 8.0 Hz, 1H), 7.17-7.18 (d, J = 4.4 Hz, 1H), 7.30-7.32 (m, 2H), 7.37-7.40 (s, 1H), 7.61-7.65 (t, J = 8 Hz, 1H), 7.78-7.80 (d, J = 8.4 Hz, 1H), 8.85-8.87 (d, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 106.17, 118.93, 122.50, 123.20, 126.89, 127.03, 128.21, 128.61, 129.42, 142.73, 147.95, 149.66, 150.25, 156.42; IR ($CHCl_3$) 3060, 3030, 2956, 2934, 2837, 1617, 1584 cm^{-1}; HRMS *m/z* 235.1001 (calcd for $C_{16}H_{13}NO$, 235.0997).

1-Phenylbenzo[*f*]quinoline (85). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 50 mg of the product (65%) as a light orange solid: mp 119-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14-7.18 (s, 1H), 7.34-7.35 (d, J = 4.8 Hz, 1H), 7.40-7.43 (m, 2H), 7.46-7.53 (m, 3H), 7.67-7.69 (d, J = 8.8 Hz, 2H), 7.87-7.89 (d, J = 8.0 Hz, 2H), 7.97-7.99 (d, J = 9.2 Hz, 1H), 8.03-8.05 (d, J = 8.8 Hz, 1H), 8.91-8.92 (d, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 123.99, 124.43, 125.56, 126.72, 128.20, 128.22, 128.33,

128.65, 128.72, 129.29, 129.79, 131.45, 133.01, 142.72, 148.45, 148.55, 149.73; IR ($CHCl_3$) 3060, 2919, 1569 cm^{-1}; HRMS *m/z* 255.1052 (calcd for $C_{19}H_{13}N$, 255.1048).

Ethyl 4-phenylquinoline-6-carboxylate (86). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 44 mg (53%) of the product as a yellow solid: mp 144-145 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37-1.41 (t, *J* = 7.2 Hz, 3H), 4.37-4.42 (q, *J* = 7.2 Hz, 2H), 7.41-7.42 (d, *J* = 4.4 Hz, 1H), 7.52-7.57 (m, 5H), 8.20-8.22 (d, *J* = 8.8 Hz, 1H), 8.31-8.33 (m, 1H), 8.71 (d, *J* = 1.2 Hz, 1H), 9.02-9.03 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.35, 61.39, 122.09, 126.06, 128.57, 128.86, 128.88, 128.91, 129.20, 129.63, 130.18, 137.34, 145.00, 150.56, 151.96, 166.31; IR ($CHCl_3$) 3060, 2919, 1569 cm^{-1}; HRMS *m/z* 277.1107 (calcd for $C_{18}H_{15}NO_2$, 277.1103).

4-Butyl-5,7-dimethoxyquinoline (88). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 55 mg (75%) of the product as a yellow solid: mp 55-56 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94-0.98 (t, *J* = 7.2 Hz, 3H), 1.40-1.46 (m, 2H), 1.60-1.64 (m, 2H), 3.16-3.19 (t, *J* = 7.6 Hz, 2H), 3.92-3.93 (d, *J* = 4.0 Hz, 2H), 6.51-6.52 (d, *J* = 2.4 Hz, 1H), 6.97-6.98 (d, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H) 8.59-8.60 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.08, 22.97, 34.04, 36.72, 55.52, 98.72, 100.92, 116.07, 120.93, 150.25, 150.32, 151.95, 158.11, 160.15 (one carbon missing due to overlap); IR ($CHCl_3$) 3394, 3001, 2956, 2938, 2867, 1628, 1587 cm^{-1}; HRMS *m/z* 245.1421 (calcd for $C_{15}H_{19}NO_2$, 245.1416).

4-(Cyclohex-1-en-1-yl)-5,7-dimethoxyquinoline (90). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 59 mg (73%) of the product as an orange solid: mp 77-79 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60-2.50 (m, 8H), 3.89 (s, 3H), 3.93 (s, 3H), 5.50-5.52 (t, *J* = 3.6 Hz, 1H), 6.51 (s, 1H), 6.89-6.90 (d, *J* = 4.4 Hz, 1H), 7.07-

7.08 (d, J = 2.4 Hz, 1H), 8.65-8.66 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.34, 23.18, 25.38, 31.07, 55.57, 56.02, 99.12, 100.43, 115.25, 119.93, 122.37, 141.31, 150.38, 150.81, 151.23, 157.10, 160.58; IR ($CHCl_3$) 3216, 3361, 3001, 2930, 2856, 2834, 1624, 1587 cm^{-1}; HRMS m/z 269.1419 (calcd for $C_{17}H_{19}NO_2$, 269.1416).

4-(Cyclohex-1-en-1-yl)-2-methylquinoline (91). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 25 mg (38 %) of the product as a light brown oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76-1.87 (m, 4H), 2.27-2.37 (m, 4H), 2.71 (s, 3H), 5.83 (s, 1H), 7.08 (s, 1H), 7.42-7.46 (t, J = 7.6 Hz, 1H), 7.63-7.66 (d, J = 7.6 Hz, 1H), 7.95-8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.11, 22.99, 25.38, 25.46, 30.31, 120.38, 125.04, 125.25, 125.50, 128.77, 128.99, 129.11, 135.49, 148.35, 151.41, 158.66; IR ($CHCl_3$) 3060, 2928, 2860, 2838, 1593 cm^{-1}; HRMS m/z 223.1364 (calcd for $C_{16}H_{17}N$, 223.1361).

4-(2-Bromophenyl)-8-methoxy-5-nitroquinoline (92). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford 70 mg of the product (65%) as a light yellow solid: mp 183-186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21 (s, 3H), 7.05-7.07 (d, J = 8.4 Hz, 1H), 7.16-7.18 (m, 1H), 7.27-7.31 (m, 1H), 7.34-7.36 (m, 1H), 7.55-7.56 (d, J = 4.0 Hz, 1H), 7.71-7.69 (d, J = 8.0 Hz, 1H), 7.94-7.96 (d, J = 8.4 Hz, 1H), 9.09-9.10 (d, J = 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.93, 105.26, 120.61, 122.00, 125.77, 127.16, 127.41, 129.91, 130.22, 133.38, 138.80, 140.51, 144.99, 149.61, 159.17; IR ($CHCl_3$) 3067, 1617, 1513, 1494 cm^{-1}; HRMS m/z 357.9957 (calcd for $C_{16}H_{11}BrN_2O_3$, 357.9953).

4-(4-Fluorophenyl)-3-[(*E*)-2-phenylethenyl]quinoline (93). To a solution of 4-(4-fluorophenyl)-3-iodoquinoline (0.15 mmol) and β-styreneboronic acid (0.23 mmol, 1.5 equiv) in 10 mL of DMF/H_2O (V/V = 4/1) were added $PdCl_2(PPh_3)_2$ (2.0 mg, 5 mol %) and K_2CO_3 (0.30 mmol, 2.0 equiv). The resulting mixture was heated under an N_2 atmosphere at

100 °C for 2 h. The mixture was cooled to room temperature and diluted with 25 ml of ether, washed with 25 mL of satd aq NaCl, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 35.4 mg (73%) of the product as a light yellow solid: mp 178-180 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (d, J = 16.5 Hz, 1H), 7.23-7.38 (m, 11H), 7.45-7.52 (m, 2H), 7.65-7.70 (m, 1H), 8.15 (d, J = 8.4 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 115.68, 115.89, 124.38, 126.26, 126.72, 127.10, 127.45, 128.15, 128.24, 128.80, 129.04, 129.61, 131.44, 131.72, 131.76, 131.94, 132.02, 136.92, 144.02, 147.31, 148.47, 161.49, 163.96; IR ($CHCl_3$) 2922, 1605, 1514, 1499 cm^{-1}; HRMS *m/z* 325.1272 (calcd for $C_{23}H_{16}FN$, 325.1267).

Acknowledgements. We gratefully acknowledge the National Institute of General Medical Sciences (GM 070620) for support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. for donations of palladium acetate.

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Chapter 3. Synthesis of Naphthalenes and 2-Naphthols by the Electrophilic Cyclization of Alkynes

Based on a paper to be submitted to the *Journal of Organic Chemistry*

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Abstract

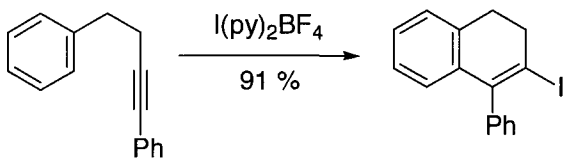
A wide variety of substituted naphthalenes are readily prepared regioselectively under mild reaction conditions by the 6-*endo*-dig electrophilic cyclization of appropriate arene-containing propargylic alcohols by ICl, I_2, Br_2, NBS, and PhSeBr. 3-Iodo-2-naphthols have also been prepared in excellent yields by cyclization of analogous 1-aryl-3-alkyn-2-ones. This methodology readily accommodates various functional groups and has been successfully extended to the synthesis of substituted carbazoles and dibenzothiophenes.

Introduction

Polysubstituted naphthalenes and 2-naphthols have played an important role in the chemical and pharmaceutical industries.[1] The discovery of technologically promising electronic and optical properties in fused aromatic compounds underscores the importance of new synthetic routes to such systems.[2] Therefore, the development of new and efficient methodologies for the regioselective synthesis of polysubstituted naphthalene derivatives has attracted much attention.[3] A variety of methods have been reported, including (i) the traditional stepwise introduction of substituents through electrophilic aromatic substitutions;[4]

(ii) [4+2] cycloaddition;[5] (iii) annulation of arenes bearing an unsaturated carbonyl side chain;[6] (iv) reaction of aryl halides or arylmetal compounds with alkynes using transition metals;[7] (v) annulation of arynes with alkynes;[8] (v) annulation via Fischer carbenes (the Dötz reaction);[9] and (vi) Lewis acid-catalyzed cyclization of carbonyl compounds or epoxides with alkynes.[10] These methods sometimes involve relatively harsh reaction conditions, expensive catalysts and substrates, which require multistep synthesis. In some cases, the reactions also produce a mixture of isomers.

Recently, we and others have developed efficient methods for the synthesis of various carbo- and heterocyclic compounds through electrophilic cyclization of appropriate *ortho*-functionalized aromatic acetylenes.[11] Relatively little work[12] has been carried out on the intramolecular electrophilic cyclization of alkynes onto arenes. Barluenga has reported one example of the electrophilic carbocyclization of 1,4-diphenyl-1-butyne to 1,2-dihydronaphthalene utilizing expensive $I(py)_2BF_4$ (eq 1).[12a] The scope of this process has yet to be investigated, but the conversion of such 1,2-dihydronaphthalenes to naphthalenes is not always easy,[13] especially when considerable functionality is present.



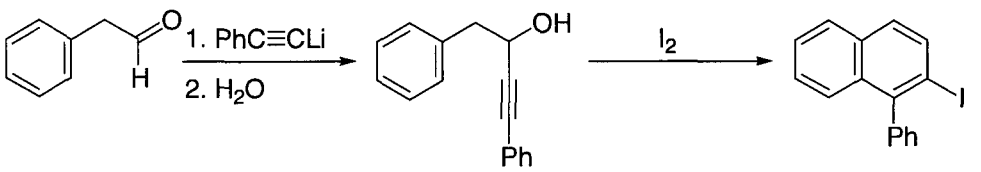
(1)

Herein, we report our results on the electrophilic cyclization of arylalkynes to naphthalenes and naphthols. This chemistry generally produces good to excellent yields of the desired arenes under very mild reaction conditions, accommodates various functional groups, and has been successfully extended to systems containing heterocyclic rings.

Results and Discussion

We envisioned that hydroxydihydronaphthalenes might be easily transformed to the corresponding naphthalenes through acid-catalyzed dehydration.[14] Thus, we chose to investigate the cyclization of appropriate benzylic-substituted propargylic alcohols, such as **1** (Scheme 1). These alcohols are easily prepared in excellent yields by the reaction of lithium acetylides and the corresponding 2-arylacetaldehydes.[15]

Scheme 1



1 **2**

We first examined the reaction of alkynol **1** with I_2 and were delighted to find that the desired 2-iodonaphthalene **2** was formed exclusively in a 75% yield after 0.5 h when using 0.3 mmol of **1**, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in MeCN at ambient temperature (Table 1, entry 1). None of the 5-*exo*-dig cyclization product was detected. Reducing the amount of I_2 to 2 equiv resulted in an incomplete reaction after 48 h. The addition of $NaHCO_3$ did improve the yield in this reaction (compare entries 1 and 2), although it is only a marginal effect.

To explore the scope of this chemistry, other electrophiles have also been examined (entries 3-6). The reaction with ICl was complete upon addition of the ICl and gave a higher yield of product **2** than the reaction with I_2 (entry 3). 2-Bromonaphthalenes

Table 1. Synthesis of Naphthalenes and Naphthols by Electrophilic Cyclization

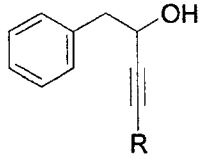
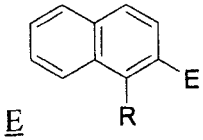
entry	substrate		electrophile	product(s)		% yield
						
1	R = Ph	**1**	I_2[a]	I	**2**	75
2			I_2[b]	I	**2**	71
3			ICl[c]	I	**2**	93
4			Br_2[d]	Br	**3**	89
5			NBS[e]	Br	**3**	40
6			PhSeBr[d]	PhSe	**4**	36[f]
7	R = *p*-$MeOC_6H_4$	**5**	I_2[a]	I	**6**	75
8	R = *p*-$CH_3COC_6H_4$	**7**	I_2[a]	I	**8**	54[g]
9			ICl	I	**8**	92
10	R = 2-thienyl	**9**	I_2[a]	I	**10**	94

Table 1. Continued

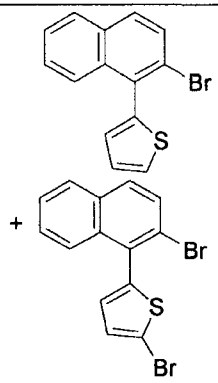
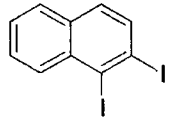
entry	substrate		electrophile	product(s)	E		% yield
11	R = 2-thienyl	**9**	Br_2[d]			**11** + **12**	45 + 36
12	R = 1-cyclohexenyl	**13**	I_2[a]		I	**14**	69
13	R = *n*-Bu	**15**	I_2[a]		I	**16**	35
14			ICl[c]		I	**16**	75
15	R = cyclohexyl	**17**	ICl[c]		I	**18**	90
16	R = $SiMe_3$	**19**	I_2[a]			**20**	0
		19	ICl[c]			**21**	50

Table 1. Continued

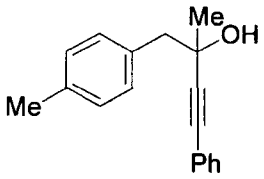
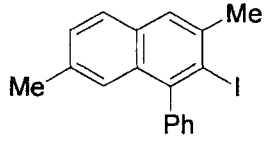
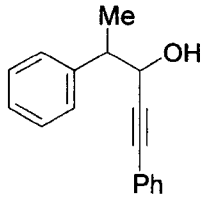
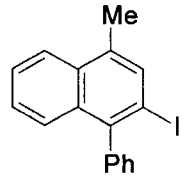
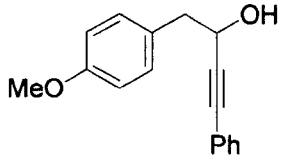
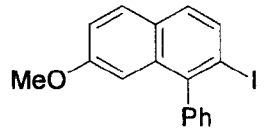
entry	substrate		electrophile	product(s)	E		% yield
17	R = OEt	**22**	I_2[a]		I	**23**	22
18		**22**	ICl[c]		I	**23**	30
19		**22**	ICl[h]		I	**23**	54
20	R = CO_2Et	**24**	I_2[a]		I	**25**	0
21		**26**	I_2[a]			**27**	78
22		**28**	I_2[a]			**29**	76
23		**30**	I_2[b]			**31**	90

Table 1. Continued

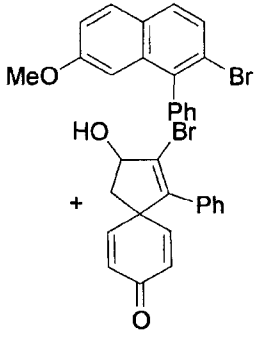
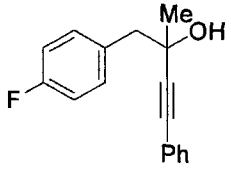
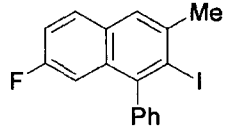
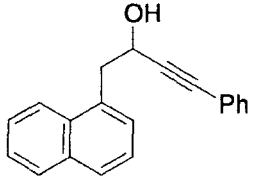
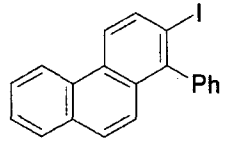
entry	substrate	electrophile	product(s)	% yield
24	**30**	Br_2[b]		**32** 55 + + **33** 25
25		**34**	I_2[a]		**35** 79
26		**36**	I_2[a]		**37** 70

Table 1. Continued

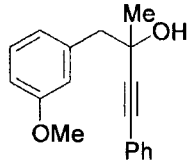
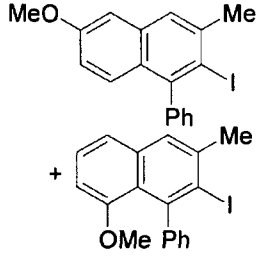
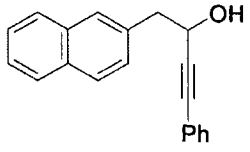
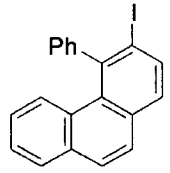
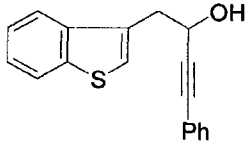
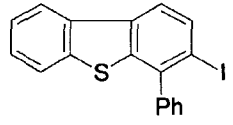
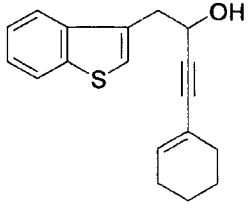
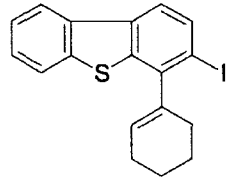
entry	substrate		electrophile	product(s)		% yield
27		**38**	I_2[a]		**39** + **40**	83 + 12
28		**41**	I_2[a]		**42**	75
29		**43**	I_2[a]		**44**	83
30		**45**	I_2[a]		**46**	74

Table 1. Continued

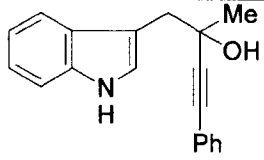
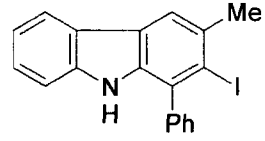
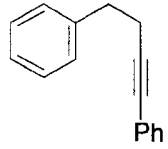
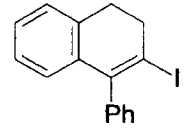
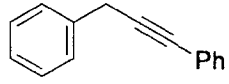
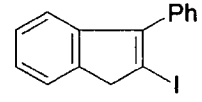
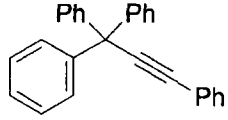
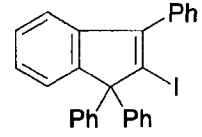
entry	substrate		electrophile	product(s)		% yield
31		**47**	I_2[a]		**48**	18
32		**47**	ICl[b]		**48**	50
33		**49**	I_2[a]		**50**	76
34		**51**	I_2[a]		**52**	0
35		**51**	ICl[b]		**52**	0
36		**53**	ICl[b]		**54**	0

Table 1. Continued

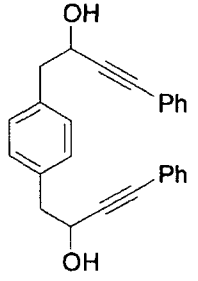
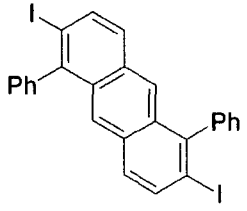
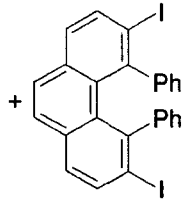
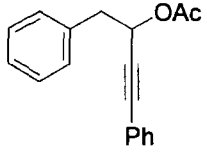
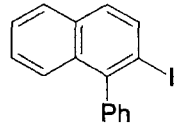
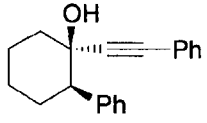
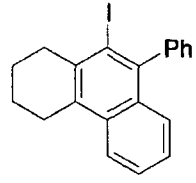
entry	substrate	electrophile	product(s)		% yield
37		**55**	I_2[a]		**56**	32
				+	+
				**57**	20
38		**58**	I_2[a,i]		**2**	51
39		**59**	I_2[a]		**60**	72

Table 1. Continued

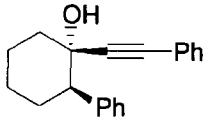
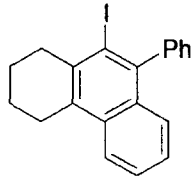
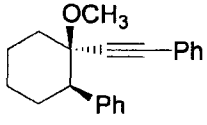
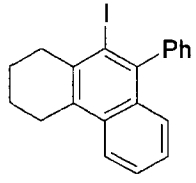
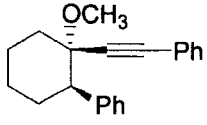
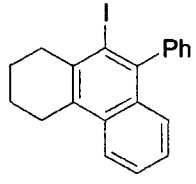
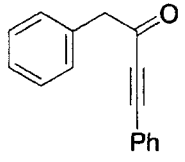
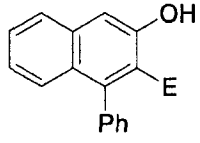
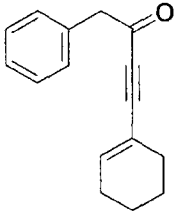
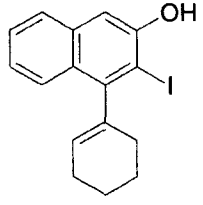
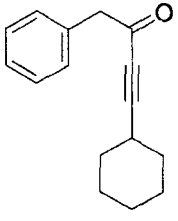
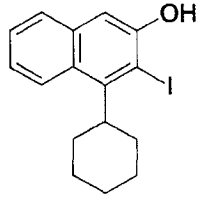
entry	substrate		electrophile	product(s)	E		% yield
40		**61**	I_2[a]			**60**	99
41		**62**	I_2[a]			**60**	99
42		**63**	I_2[a]			**60**	90
43		**64**	I_2[a]		I	**65**	45
44			I_2[b]		I		78
45			ICl[b]		I		98
46			Br_2[b]		Br	**66**	trace

Table 1. Continued

entry	substrate		electrophile	product(s)		% yield
47		**67**	ICl[b]		**68**	65
48		**69**	ICl[b]		**70**	79

[a] The reactions were run under the following conditions: 0.3 mmol of the propargylic alcohol, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN were stirred at room temperature. [b] No $NaHCO_3$ was employed. [c] 2 Equiv of ICl in 1 mL of CH_3CN was added dropwise to 0.3 mmol of propargylic alcohol and 2 equiv of $NaHCO_3$ in 2 mL of CH_3CN at room temperature. [d] 2 Equiv of Br_2 or PhSeBr in 1 mL of CH_3CN was added dropwise to 0.3 mmol of propargylic alcohol and 2 equiv of $NaHCO_3$ in 2 mL of CH_3CN at room temperature. [e] 0.9 Mmol of NBS and 0.3 mmol of propargylic alcohol in 5 mL of CH_3CN were stirred at 50 °C for half an hour. [f] The product formed from simple addition of PhSeBr to the triple bond was obtained in a 53% yield. [g] The reaction took 48 h. [h] 2 Equiv of ICl in 1 mL of CH_2Cl_2 was added dropwise to 0.3 mmol of propargylic alcohol **21** and 2 equiv of $NaHCO_3$ in 2 mL of CH_2Cl_2 at –78 °C. [i] 3 Equiv of $NaHCO_3$ was employed.

can be obtained by using either Br_2 or NBS as the electrophile. An excellent 89% yield was provided by Br_2 at room temperature (entry 4). The reaction with NBS proceeded only at a higher temperature (50 °C) and afforded a lower yield of **3** (entry 5). Cyclization with PhSeBr provided a 36% yield of 2-naphthyl phenyl selenide, together with a 53% yield of the product of simple addition of PhSeBr to the triple bond (entry 6).

Alkynes bearing an electron-rich aromatic ring and an acid-sensitive heterocycle, such as a thiophenyl group, reacted well with I_2 to provide the desired 1,2-disubstituted iodonaphthalenes in excellent yields (entries 7 and 10). None of the products of direct substitution on the electron-rich aromatic ring in these two examples were observed. Although the yield utilizing I_2 was only moderate for substrate **7** (entry 8), presumably because the ketone group decreases the electron-density of the aromatic ring, the desired conversion could be significantly improved by using ICl as the electrophile (entry 9). In the case of substrate **9**, cyclization with 2 equiv of Br_2 resulted in a 45% yield of the monobrominated product **11** and a 36% yield of the dibromo product **12**, which bears an extra Br on the 5-position of the thiophene (entry 11). The reaction with I_2 proceeded smoothly when a vinylic group was present on the alkyne terminus (entry 12). While only a 35% yield of 1-*n*-butyl-2-iodonaphthalene was isolated from the reaction of 1-phenyl-3-octyn-2-ol and I_2, a higher 75% yield was again obtained when ICl was employed (compare entries 13 and 14). An even better yield was obtained from an alkyne bearing a secondary alkyl group on the alkyne terminus (entry 15). The sterically hindered trimethylsilyl-substituted alkyne **19** was cyclized without difficulty when treated with ICl (entry 16), but the only product observed was 1,2-diiodonaphthlene in which the trimethylsilyl group was substituted by an iodine moiety. No reaction occurred with this alkyne when using I_2 as the

electrophile. The synthesis of 1-ethoxy-2-iodonaphthalene from the corresponding ethoxy-substituted alkyne was not very successful using either I_2 or ICl as electrophiles under our standard reaction conditions (entries 17 and 18). Only low yields have been obtained. However, by lowering the reaction temperature of the ICl reaction, we were able to improve the yield to 54% (entry 19). No cyclization product was observed when an ester-substituted alkyne was allowed to react with I_2 (entry 20).

To explore the effect of substituents in the side chain, a tertiary alcohol **26** was examined under our standard reaction conditions (entry 21). The presence of a methyl group did not hamper either the cyclization or the dehydration. Thus, regiospecific 2,3,4-trisubstituted naphthalenes can be readily synthesized in good yield in a single step using this methodology. The presence of methyl substitution on the benzylic position did not affect the overall yield either (entry 22). This allows a very direct approach to 1,2,4-trisubstituted naphthalene **29**.

We next investigated the cyclization onto substituted arenes. Treatment of 1-(4-methoxyphenyl)-4-phenylbut-3-yn-2-ol (**30**) with I_2 under our standard reaction conditions afforded cyclization product **31** in a 90% yield (entry 23). A lower yield of bromonaphthalene **32** was obtained because of competitive *ipso*-cyclization to spirocycle **33**.[16] Cyclization onto an aromatic ring substituted by a strong electron-withdrawing group, such as a fluorine group (entry 25), proceeded smoothly, affording an excellent yield of the desired naphthalene, even though the fluorine significantly lowers the nucleophilicity of the aromatic ring undergoing substitution. Iodocyclization onto a naphthalene ring afforded the corresponding 2-iodophenanthrene in a good yield (entry 26).

The regioselectivity of this cyclization has also been explored. Cyclization onto 3-methoxyphenyl alkynol **38** was quite regioselective, affording a 7:1 regioisomeric mixture of **39** and **40** in an excellent overall yield (entry 27). The isomer **39** formed by cyclization onto the less hindered position *para* to the methoxy group is the major product. Only one isomer was observed in the cyclization of 2-naphthyl alkynol **41**; ring closure occurred selectively on the one position of the naphthalene ring (entry 28). This is rather surprising, since analogous iodocyclization of 2-naphthyl-3-phenylpropargylamine gave exclusively the aromatic amine formed by cyclization onto the three position of the naphthalene.[12e] Clearly, electronic effects favor cyclization to **42** over cyclization to the less hindered 3-position of the naphthalene.

We were particularly interested in extending these cyclizations to alkynes containing important electron-rich heteroaromatic rings, such as benzothiophenes and indoles. As exemplified in entries 29 and 30, both benzothiophene derivatives **44** and **46** undergo I_2-induced carbocyclization to the corresponding dibenzothiophenes in excellent yields. However, only an 18% yield of iodocarbazole **48** was obtained under our standard I_2 cyclization conditions without formation of any significant side products (entry 31). The yield of this cyclization could be improved to 50% when ICl was used as the electrophile (entry 32). These benzannulations all start from readily available precursors, involve very simple synthetic manipulations with highly regio-controlled ring formation, and provide the desired products in good to excellent yields.

Our protocol utilizing much more economical and convenient to handle I_2 can also be employed in the synthesis of 1,2-dihydronaphthalenes (entry 33), considerably simplifying the procedure developed earlier by Barluenga using an iodonium reagent.[12a] In comparison,

the attempted cyclization to iodoindenes through a 5-*endo*-dig cyclization failed completely using either I_2 or ICl (entries 34-36). In all cases, 1,2-adducts formed by direct I_2 or ICl addition to the triple bond were obtained.

The facility with which this carbocyclization process occurs encouraged us to attempt a double cyclization. The double cyclization of diyne **55** afforded a 32% yield of diiodoanthracene **56** and a 20% yield diiodophenanthrene **57** in a decent overall yield.

A propargylic acetate **58** has also been successfully employed in this process, although more base and a longer reaction time were required (entry 38). None of the corresponding dihydronaphthalene acetate was detected.

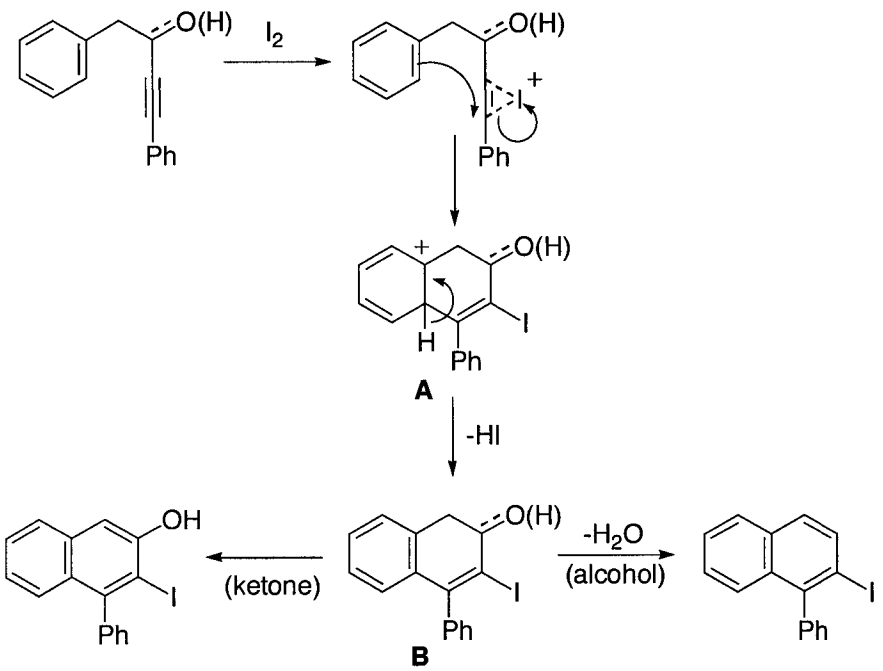
The synthetic utility of this protocol has also been demonstrated in the preparation of iodotetrahydrophenanthrene **60**. Both *cis*- and *trans*-2-phenyl-1-(phenylethynyl)cyclohexanol (**59** and **61**) can be efficiently cyclized under our standard reaction conditions to provide the desired arene **60** in a 72% (from the *cis*-cyclohexanol) or quantitative yield (from the *trans*-cyclohexanol) (entries 39 and 40). Furthermore, compound **60** can also be obtained from the corresponding methyl ethers of **59** and **61** in almost quantitative yields (entries 41 and 42). Obviously the relative stereochemistry of the alcohols or ethers in these systems has little effect on the overall success of these cyclizations. It should be pointed out that during these cyclizations no spots corresponding to the intermediate dihydronaphthalenes could be detected by TLC analysis. The starting materials were gradually consumed, while the desired product was generated at the same time. The anticipated dihydronaphthalenes either immediately undergo elimination by the I_2 during the reaction or by the silica gel during the thin layer chromatography.

In comparison, the reaction of 1,4-diphenylbut-3-yn-1-ol bearing the OH group now on the benzylic position instead of the propargylic position became very sluggish under the I_2 cyclication conditions with or without base when starting from. Most of the alkynol was left after 24 h and the desired naphthalene **2** was obtained in only a 20 % yield.

Interestingly, 3-iodo-4-phenyl-2-naphthol (**64**) can be readily prepared by analogous cyclization of the appropriate alkynone **65** (entries 43-46). An initial experiment in the presence of base indicated a rather messy reaction with several unidentified side products (entry 43). We assume that those side products might have come from base-induced iodination of the ketone and subsequently found that by simple removal of the base, the yield was improved dramatically to 78% (entry 44). An almost quantitative yield was obtained using ICl as the electrophile and no base (entry 45). However, only a trace of the bromonaphthol derivative **66** was generated when we employed Br_2 as the electrophile. This is a general approach to iodonaphthols as it is also compatible with both vinylic and alkyl substitution on the alkyne (entries 47 and 48).

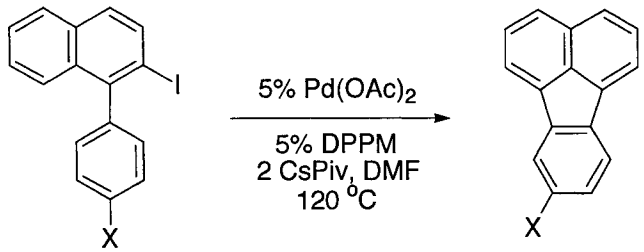
We believe that this 6-*endo*-dig cyclization proceeds by *anti* attack of the electrophile and the aromatic ring on the alkyne to produce a cationic intermediate **A** (Scheme 2). Deprotonation of **A** affords the hydroxydihydronaphthalene **B**. Dehydration of the presumed intermediate **B** to the naphthalene is evidently rapid even in the presence of a base, since intermediates, such as **B,** have not been observed. The cyclization of alkynones is believed to follow the same pathway, except that tautomerization of the ketone intermediate to the naphthol affords the final product.

Scheme 2

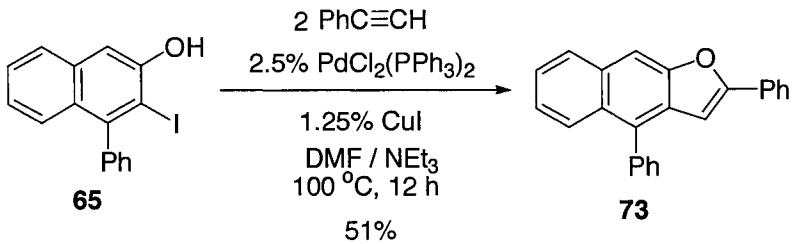


Halogenated naphthalenes and naphthols are very valuable intermediates in organic synthesis, a status much enhanced by recent developments in radical chemistry and especially in transition metal-catalyzed reactions.[17] For example, halonaphthalenes and naphthols are useful starting materials for palladium-catalyzed coupling reactions,[18] Pd migration to fused tricyclic compounds,[19] annulation to naphtha[2,3-*b*]furans[20] and polycyclic aromatic hydrocarbons,[21] carbonylation to benzo[*c*]flourenones,[22] and carbonylative annulation of alkynes to coumarins.[23] Some examples of the Pd migration and alkyne annulation chemistry are illustrated in Scheme 3.

Scheme 3



X	time (h)	% yield
OMe (**6**)	24	65 (**71**)
Ac (**8**)	84	64 (**72**)



Conclusions

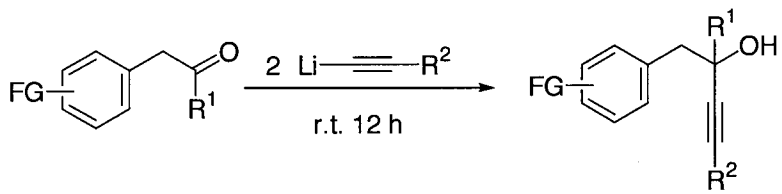
In summary, we have developed a new, very efficient protocol to effect the regioselective cyclization of simple aromatic acetylenes to multisubstituted 2-iodonaphthalenes and 3-halo-2-naphthols under very mild reaction conditions. This methodology accommodates various functional groups and generally affords the products in good yields. It has also been successfully applied to the cyclization of heterocyclic systems. Finally, the resulting halogen-containing products can be readily elaborated to more complex products using known organopalladium chemistry.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially

prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

Synthesis of Starting Materials. Compounds **1, 13, 15, 17, 19, 22, 24, 26, 28, 30, 34, 36, 38, 41** and **47** were prepared by the condensation of an α-arylacetaldehyde or an α-arylacetone with the corresponding lithium acetylides. A typical reaction is



described below. To a solution of the acetylene in anhydrous THF was added 1 equiv of *n*-BuLi at 0 °C under an Ar atmosphere. The resulting solution was stirred at that temperature for 1 h. Then 0.5 equiv of the α-arylacetaldehyde or α-arylacetone in THF was added by syringe. The reaction mixture was kept under the inert atmosphere and stirred for 12 h while it warmed up to ambient temperature. The mixture was then quenched by adding satd aq NH_4Cl and extracted twice with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel.

1,4-Diphenylbut-3-yn-2-ol (1). The indicated compound was prepared as a light yellow oil in a 75% yield from the coupling of phenylacetylene with phenylacetaldehyde. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. The spectral properties were identical with those previously reported.[24]

4-(Cyclohex-1-enyl)-1-phenylbut-3-yn-2-ol (13). The indicated compound was prepared as a light yellow oil in a 65% yield from the reaction of 1-ethynylcyclohexene and phenylacetaldehyde. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52-1.59 (m, 4H), 2.03-2.05 (m, 4H), 2.57-2.59 (m, 1H), 2.95-2.98 (d, J = 6.3 Hz, 2H), 4.61-4.63 (m, 1H), 6.04-6.05 (m, 1H), 7.20-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.77, 22.56, 25.90, 29.36, 44.60, 63.86, 87.31, 87.80, 120.43, 126.98, 128.52, 130.17, 135.40, 137.22; IR ($CHCl_3$) 3420, 2941, 2372, 1653 cm^{-1}; HRMS *m/z* 226.1360 (calcd for $C_{16}H_{18}O$, 226.1358).

1-Phenyloct-3-yn-2-ol (15). The indicated compound was prepared as a colorless oil in a 50% yield from the reaction of 1-hexyne and phenylacetaldehyde. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. The spectral properties were identical with those previously reported.[25]

4-Cyclohexyl-1-phenylbut-3-yn-2-ol (17). The indicated compound was prepared as a colorless oil in a 52% yield from the reaction of cyclohexylacetylene and phenylacetaldehyde. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29-1.81 (m, 10H), 2.41 (m, 1H), 2.82 (m, 1H), 3.00-3.02 (d, J = 6.3 Hz, 2H), 4.56-4.61 (m, 1H), 7.26-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.12, 26.17, 29.28, 32.85, 44.83, 63.62, 81.02, 90.66, 126.91, 128.46, 130.20, 137.41; IR ($CHCl_3$) 3395, 3031, 2927, 2857, 2237 cm^{-1}; HRMS *m/z* 228.1516 (calcd for $C_{16}H_{20}O$, 228.1514).

1-Phenyl-4-(trimethylsilyl)but-3-yn-2-ol (19). The indicated compound was prepared as a light yellow oil in a 70% yield from the reaction of (trimethylsilyl)acetylene and phenylacetaldehyde. The reaction mixture was chromatographed using 10:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 9H), 2.40-2.60 (br s, 1H), 3.00-3.02

(d, J = 6.3 Hz, 2H), 4.54-4.58 (t, J = 6.3 Hz, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.01, 44.16, 63.69, 90.55, 106.35, 127.02, 128.44, 130.12, 136.75; IR ($CHCl_3$) 3430, 2966, 2367, 1948 cm^{-1}; HRMS *m/z* 218.1131 (calcd for $C_{13}H_{18}OSi$, 218.1127).

4-Ethoxy-1-phenylbut-3-yn-2-ol (22). The indicated compound was prepared as an orange oil from the reaction of ethoxyethyne and phenylacetaldehyde in a 71% yield. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20-1.27 (t, J = 7.2 Hz, 3H), 2.50 (br s, 1H), 2.89-2.91 (d, J = 7.8 Hz, 2H), 3.93-4.00 (q, J = 7.8 Hz, 2H), 4.52-4.53 (m, 1H), 7.18-7.28 (m, 5H), 7.34-7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.59, 39.48, 45.32, 63.39, 74.84, 94.77, 126.86, 128.50, 130.09, 137.72; IR ($CHCl_3$) 3394, 3030, 2930, 2262, 1495 cm^{-1}; HRMS *m/z* 190.0996 (calcd for $C_{12}H_{14}O_2$, 190.0994).

2-Methyl-1-(4-methylphenyl)-4-phenylbut-3-yn-2-ol (26). The indicated compound was prepared as a light yellow oil from the reaction of phenylacetylene and (4-methylphenyl)acetone in a 100% yield. The reaction mixture was chromatographed using 4:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 2.28 (s, 1H), 2.58 (s, 1H), 2.96-2.98 (d, J = 4.8 Hz, 2H), 7.02-7.10 (d, J = 7.8 Hz, 2H), 7.21-7.26 (m, 5H), 7.34-7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.48, 29.80, 49.76, 68.85, 84.78, 93.19, 123.23, 128.60, 128.63, 129.18, 131.08, 131.95, 133.75, 136.78; IR ($CHCl_3$) 3553, 3401, 2927, 2867, 1517, 1443 cm^{-1}; HRMS *m/z* 250.1363 (calcd for $C_{18}H_{18}O$, 250.1358).

1,4-Diphenylpent-1-yn-3-ol (28). The indicated compound was prepared as a light yellow oil from the reaction of phenylacetylene and 2-phenylpropanal in a 85% yield (diastereomeric mixture). The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42-1.46 (m, 3H), 2.29-2.32 (m, 1H), 2.09-

3.13 (m, 1H), 4.62-4.64 (m, 1H), 7.20-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.66, 17.13, 46.30, 46.77, 67.96, 68.29, 86.66, 89.15, 89.15, 123.00, 127.32, 127.35, 128.53, 128.55, 128.59, 128.60, 128.63, 128.70, 128.74, 128.76, 128.94, 131.95, 131.98, 132.01, 142.10, 142.36; IR ($CHCl_3$) 3546, 3364, 3064, 3030, 2975, 2912, 1495, 1454 cm^{-1}; HRMS *m/z* 236.1205 (calcd for $C_{17}H_{16}O$, 236.1201).

1-(4-Methoxyphenyl)-4-phenylbut-3-yn-2-ol (30). To a cooled suspension (ice bath) of PCC (4.31 g, 20 mmol) in CH_2Cl_2 (200 mL) was slowly added a solution of 2-(4-methoxyphenyl)ethanol (15 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at that temperature for 2 h, then warmed up to rt for another 2 h. The mixture was filtered through celite and the solvents were removed under vacuum. The reaction mixture was chromatographed using 5:1 hexane/EtOAc to give the (4-methoxyphenyl)acetaldehyde as a colorless oil in 75% yield. To a solution of phenylacetylene (10 mmol) in 30 mL of anhydrous THF at 0 °C was added *n*-BuLi (10 mmol, 2.5M in hexane) under N_2, and the resulting solution was stirred at that temperature for 1 h. Then (4-methoxyphenyl)acetaldehyde (5 mmol) in 10 ml of THF was added to the solution under an N_2 atmosphere. The resulting solution was stirred at rt for 2 h. Brine (30 mL) was then added to quench the reaction and the solution was extracted twice using diethyl ether (2 x 30 mL). The solvents were removed under vacuum, and the reaction mixture was chromatographed using 5:1 hexane/EtOAc to obtain alkynol **30** as a light orange oil in an 80% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.91 (s, 1H), 2.99-3.01 (d, J = 6.3 Hz, 2H), 3.71 (s, 3H), 4.71 (m, 1H), 6.80-6.83 (d, J = 8.7 Hz, 2H), 7.16-7.26 (m, 5H), 7.35-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.57, 55.50, 64.07, 85.95, 90.18, 114.09, 122.96, 128.61,

128.70, 129.08, 131.21, 131.95, 158.79; IR (CH_2Cl_2) 3310, 1609 cm^{-1}; HRMS *m/z* 252.1154 (calcd for $C_{17}H_{16}O_2$, 252.1150).

1-(4-Fluorophenyl)-2-methyl-4-phenylbut-3-yn-2-ol (34). The indicated compound was prepared as a light yellow oil in a 92% yield from the reaction of phenylacetylene and (4-fluorophenyl)acetone. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.62 (s, 3H), 2.04 (br s, 1H), 2.97-3.06 (m, 2H), 7.00-7.04 (m, 2H), 7.28-7.37 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.63, 48.89, 68.49, 84.86, 92.20, 114.86, 115.07, 122.56, 128.36, 128.47, 131.02, 131.58, 132.20, 132.23, 132.28, 160.99, 163.43 (the extra peaks are due to F splitting); IR ($CHCl_3$) 3416, 3056, 2991, 2937, 1713, 1608, 1508 cm^{-1}; HRMS *m/z* 254.1111 (calcd for $C_{17}H_{15}FO$, 254.1107).

1-(1-Naphthyl)-4-phenylbut-3-yn-2-ol (36). The indicated compound was prepared as a light yellow oil in a 90% yield from the reaction of phenylacetylene and 1-naphthylacetaldehyde, which was prepared by the Swern oxidation of 2-(1-naphthyl)ethanol.[26] The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.06-2.08 (m, 2H), 3.58-3.62 (m, 2H), 4.96-5.02 (m, 1H), 7.25-7.56 (m, 9H), 7.78-7.89 (m, 2H), 8.14-8.17 (d, *J* = 8.04, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.35, 63.43, 86.04, 89.76, 122.63, 124.04, 125.58, 125.81, 126.26, 127.96, 128.41, 128.51, 128.60, 129.00, 131.81, 132.44, 132.91, 134.10; IR ($CHCl_3$) 3361, 3054, 2933, 1489 cm^{-1}; HRMS *m/z* 272.1204 (calcd for $C_{20}H_{16}O$, 272.1201).

1-(3-Methoxyphenyl)-2-methyl-4-phenylbut-3-yn-2-ol (38). The indicated compound was prepared as a light yellow oil in a 95% yield from the reaction of phenylacetylene and (3-methoxyphenyl)acetone. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 2.00-2.10 (br s, 1H),

2.96-3.09 (q, J = 12.9 Hz, 2H), 3.77 (s, 3H), 6.82-6.86 (m, 1H), 6.95-6.98 (m, 2H), 7.23-7.32 (m, 4H), 7.36-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.63, 49.80, 55.16, 68.36, 84.57, 92.47, 112.67, 116.30, 122.67, 123.15, 128.26, 128.32, 129.11, 131.58, 137.82, 159.42; IR ($CHCl_3$) 3476, 3061, 2986, 2942, 2842, 1608 cm^{-1}; HRMS *m/z* 266.1310 (calcd for $C_{18}H_{18}O_2$, 266.1307).

1-(2-Naphthyl)-4-phenylbut-3-yn-2-ol (41). To the solution of 2-(2-naphthyl)ethanol (2 mmol) in 10 mL of CH_2Cl_2 was added Dess-Martin periodinane (2 mmol). The mixture was stirred for 2 h. The reaction was diluted with another 20 mL of CH_2Cl_2. The organic layer was consequently washed with 20 mL of aq satd $Na_2S_2O_3$, 20 mL of aq satd $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel by 10:1 hexane/EtOAc to afford 2-naphthylacetaldehyde in a 98% yield. Compound **41** was prepared by the reaction of phenylacetylene and 1-naphthylacetaldehyde as a light yellow oil. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.11-2.13 (d, J = 5.9 Hz, 1H), 3.28-3.30 (m, 2H), 4.89-4.95 (m, 1H), 7.27-7.52 (m, 8H), 7.81-7.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.52, 63.88, 86.22, 89.64, 122.72, 125.89, 126.32, 127.88, 127.91, 128.21, 128.39, 128.54, 128.72, 128.82, 131.89, 132.74, 133.69, 134.27; IR ($CHCl_3$) 3349, 3056, 2927, 2867, 1602, 1491 cm^{-1}; HRMS *m/z* 272.1204 (calcd for $C_{20}H_{16}O$, 272.1201).

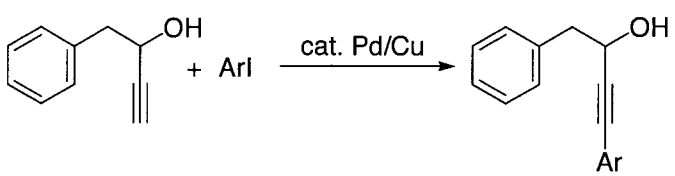
1-(Benzothien-3-yl)-4-phenylbut-3-yn-2-ol (43). A solution of 3-benzothienylacetic acid (6.6 mmol) in 10 mL of anhydrous diethyl ether was slowly added to a stirred solution of LAH (11.2 mmol) in 50 mL of diethyl ether at 0 °C. The ice bath was removed and the solution was stirred for 4 h, while it was allowed to warm to room temperature. Water was

slowly added to decompose the excess LAH (caution - gas evolution and an exotherm). The organic layer was subsequently washed with 10% H_2SO_4, aq satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum to give 3-(2-hydroxyethyl)benzothiophene, which was used directly in the next step. To the solution of 3-(2-hydroxyethyl)benzothiophene in 30 mL of CH_2Cl_2 was added PCC (8.6 mmol) at 0 °C. The mixture was stirred for 4 h at 0 °C until all of the alcohol was consumed. The light brown solution was filtered and the filtrate was collected. The solvent was removed and the residue was purified by chromatography on silica gel using 10:1 hexane/EtOAc to give (3-benzothienyl)acetaldehyde in a 35% overall yield. To a solution of phenylacetylene (2.0 mmol) in 20 mL of anhydrous THF was added *n*-BuLi (2.0 mmol, 2.5M in hexane) at 0 °C under an Ar atmosphere. The resulting solution was stirred at that temperature for 1 h. Then (3-benzothienyl)acetaldehyde (1.0 mmol) in 5 mL of anhydrous THF was added by syringe. The reaction mixture was kept under an inert atmosphere and stirred for 2 h. The mixture was then quenched by adding satd aq NH_4Cl and extracted twice with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using 10:1 hexane/EtOAc to give 1-(benzothien-3-yl)-4-phenylbut-3-yn-2-ol (139 mg, 50%) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (br s, 1H), 3.34-3.36 (d, J = 6.3 Hz, 2H), 4.90-4.94 (t, J = 6.3 Hz, 1H), 7.22-7.40 (m, 8H), 7.84-7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.12, 62.72, 85.98, 89.75, 122.24, 122.60, 123.14, 124.30, 124.57, 124.70, 128.54, 128.79, 131.50, 131.94, 139.37, 140.61; IR ($CHCl_3$) 3430, 3060, 1615 cm^{-1}; HRMS *m/z* 278.0772 (calcd for $C_{18}H_{14}OS$, 278.0765).

1-(Benzothien-3-yl)-4-(cyclohexen-1-yl)but-3-yn-2-ol (45). This compound was prepared using the same method as compound **43,** but coupling (3-benzothienyl)acetaldehyde and 1-ethynylcyclohexene. The crude product was purified by flash chromatography on silica gel using 5:1 hexane/EtOAc to give compound **45** (142 mg, 51%) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51-1.60 (m, 4H), 1.99-2.13 (m, 5H), 3.25-3.27 (d, J = 6.3 Hz, 2H), 4.78-7.82 (t, J = 6.3 Hz, 1H), 6.01-6.03 (m, 1H), 7.22-7.39 (m, 3H), 7.79-7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.67, 22.46, 25.85, 29.23, 37.26, 62.65, 87.05, 87.78, 120.19, 122.24, 123.06, 124.19, 124.47, 124.50, 131.68, 135.84, 139.37, 140.54; IR ($CHCl_3$) 3386, 3064, 2930, 2860, 2185, 1669, 1435 cm^{-1}; HRMS *m/z* 282.1085 (calcd for $C_{18}H_{18}OS$, 282.1078).

1-(1*H*-Indol-3-yl)-2-methyl-4-phenylbut-3-yn-2-ol (47). The indicated compound was prepared as a sticky light red oil from the reaction of phenylacetylene and 3-(1*H*-indolylacetone in a 55% yield. The reaction mixture was chromatographed using 3:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H), 2.45 (br s, 1H), 3.14-3.19 (d, J = 14.4 Hz, 1H), 3.28-3.33 (d, J = 14.4 Hz, 1H), 7.11-7.35 (m, 9H), 7.75-7.78 (d, J = 7.8 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.71, 39.93, 69.03, 83.72, 93.71, 110.82, 111.39, 119.88, 120.00, 122.31, 123.07, 124.34, 128.45, 128.62, 131.91, 136.34; IR ($CHCl_3$) 3412, 3060, 2986, 2927, 1458 cm^{-1}; HRMS *m/z* 275.1314 (calcd for $C_{19}H_{17}NO$, 275.1310).

Compounds **5**, **7**, and **9** were prepared by the Sonogashira reaction of 1-phenylbut-3-yn-2-ol with the corresponding aryl halide.



1-Phenylbut-3-yn-2-ol. To a solution of 1-phenyl-4-(trimethylsilyl)but-3-yn-2-ol (**19**, 1.20 g, 5.5 mmol) in 20 mL of MeOH was added KF (0.41 g, 7.0 mmol). After being stirred for 12 h at room temperature, the reaction was quenched by adding brine. The reaction mixture was extracted with Et_2O (2 x 30 mL). The extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford 642 mg of the product (80% yield) as a light yellow oil. The spectra properties were identical with those previously reported.[26]

General Procedure for the Coupling Reaction of 1-Phenylbut-3-yn-2-ol with Aryl Halides. To a solution of Et_3N (30 mL), $PdCl_2(PPh_3)_2$ (2 mol %), 3.0 mmol of 1-phenylbut-3-yn-2-ol, and 1.2 equiv of aryl iodide (stirring for 3 min beforehand) was added CuI (1 mol %). The reaction mixture was flushed with Ar and the flask was then sealed. The mixture was stirred at room temperature and monitored by TLC for completion (2-12 h). The resulting solution was filtered, washed with a satd aq NaCl solution, and extracted with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel.

4-(4-Methoxyphenyl)-1-phenylbut-3-yn-2-ol (5). The indicated compound was prepared as a yellow oil from *p*-iodoanisole in a 75% yield. The reaction mixture was chromatographed using 3:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 1H), 3.06-3.08 (m, 2H), 3.77 (s, 3H), 4.77 (m, 1H), 6.79-6.81 (d, J = 8.8 Hz, 3H), 7.24-7.33 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.34, 55.35, 63.78, 85.81, 88.19, 114.00, 114.70, 126.96, 128.46, 129.99, 133.19, 136.80, 159.75; IR ($CHCl_3$) 3384, 3060, 2929, 2837, 1606 cm^{-1}; HRMS *m/z* 252.1154 (calcd for $C_{17}H_{16}O_2$, 252.1150).

1-[4-(3-Hydroxy-4-phenylbut-1-ynyl)phenyl]ethanone (7). The indicated compound was prepared as a light orange oil from 4-iodoacetophenone in a 72% yield. The reaction mixture was chromatographed using 3:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 2.66 (s, 1H), 3.10-3.12 (d, J = 6.4 Hz, 2H), 4.80-4.83 (t, J = 6.4 Hz, 1H), 7.25-7.33 (m, 5H), 7.41-7.43 (d, J = 8.0 Hz, 2H), 7.84-7.86 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.69, 44.09, 63.70, 84.95, 93.06, 127.07, 127.56, 128.29, 128.51, 129.92, 131.80, 136.36, 136.51, 197.66; IR ($CHCl_3$) 3411, 3022, 2930, 2868, 1670, 1593 cm^{-1}; HRMS 264.1156 *m/z* (calcd for $C_{18}H_{16}O_2$, 264.1150).

1-Phenyl-4-(thien-2-yl)but-3-yn-2-ol (9). The indicated compound was prepared as a light brown oil from 2-iodothiophene in a 78% yield. The reaction mixture was chromatographed using 5:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (s, 1H), 3.02-3.04 (d, J = 6.4 Hz, 2H), 4.72-4.75 (t, J = 6.4 Hz, 2H), 6.87-6.90 (m, 1H), 7.12-7.16 (m, 2H), 7.21-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.12, 63.86, 79.31, 93.67, 122.63, 127.06, 127.13, 127.47, 128.55, 130.04, 132.36, 136.69; IR ($CHCl_3$) 3361, 3106, 3026, 2927, 2223, 1613 cm^{-1}; HRMS *m/z* 228.0613 (calcd for $C_{14}H_{12}OS$, 228.0609).

1,4-Diphenyl-1-butyne (49). To a solution of Et_3N (30 mL), $PdCl_2(PPh_3)_2$ (2 mol %), 4-phenyl-1-butyne (3.0 mmol), and 1.2 equiv of phenyl iodide (stirring for 3 min beforehand) was added CuI (1 mol %). The reaction mixture was flushed with Ar and the flask was then sealed. The mixture was stirred at room temperature for 12 h. The resulting solution was filtered, washed with a satd aq NaCl solution, and extracted with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using

hexane to give 1,4-diphenyl-1-butyne (84%) as a light yellow oil. The spectral properties were identical with those previously reported.[27]

1,4-Diphenyl-1-propyne (51). To a solution of Et_3N (20 mL), $PdCl_2(PPh_3)_2$ (2 mol %), 5.0 mmol of 3-phenyl-1-propyne, and 7.5 mmol of PhI (stirring for 3 min beforehand) was added CuI (1 mol %). The reaction mixture was flushed with Ar and the flask was then sealed. The mixture was stirred at room temperature for 2 h. The resulting solution was filtered, washed with a satd aq NaCl solution, and extracted with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography using hexane on silica gel. Compound **51** was obtained as a colorless oil in an 85% yield. The spectral properties were identical with those previously reported.[28]

Compound **53** was prepared according to the literature procedure.[29]

1-Phenyl-4-[4-(2-hydroxy-4-phenyl-3-butynyl)phenyl]but-3-yn-2-ol (55). 1,4-Benzenediacetic acid (6.5 mmol) in 50 mL of ethanol was mixed with 5 mL of 36N concentrated sulfuric acid. The reaction mixture was refluxed for 18 h. The ethanol was removed by vacuum and the residue was worked-up using ether and brine. The organic layer was separated, washed consequently using a satd aq $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum to give the crude product, which was purified by flash chromatography using 3:1 hexane/EtOAc to give 1,4-benzenediacetic acid diethyl ester in a 77% yield. A solution of 1,4-benzenediacetic acid diethyl ester (5.0 mmol) in 10 mL of anhydrous diethyl ether was slowly added to a stirred solution of LAH (10.0 mmol) in 30 mL of diethyl ether. The resulting mixture was refluxed for 3 h. Water was added to decompose the excess LAH. Concentrated HCl was added to

dissolve the precipitate. The organic layer was extracted with ether and washed with aq satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum to give the crude product, which was purified by flash chromatography using EtOAc to give 1,4-benzenediethanol in an 84% yield. To a solution of 1,4-benzenediethanol (1 mmol) in 10 mL of CH_2Cl_2 was added Dess-Martin periodinane (3 mmol) at r.t. The mixture was stirred 4 h at room temperature until all of the alcohol was consumed. The solution was filtered and the filtrate was collected. The solvent was removed and the residue was purified by chromatography on silica gel using 3:1 hexane/EtOAc to give 1,4-benzenediacetaldehyde in a 62% overall yield. To a solution of phenylacetylene (10.8 mmol) in 20 mL of anhydrous THF was added *n*-BuLi (10.8 mmol) at 0 °C under Ar atmosphere. The resulting solution was stirred at that temperature for 1 h. Then 1,4-benzenediacetaldehyde (2.7 mmol) in 5 mL of anhydrous THF was added by syringe. The reaction mixture was kept under an inert atmosphere and stirred for 12 h. The mixture was then quenched by the addition of satd aq NH_4Cl and extracted twice with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using 3:1 hexane/EtOAc to give compound **55** (21%) as light yellow solid: mp 144-145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 2H), 3.07-3.12 (m, 4H), 4.77-4.80 (m, 2H), 7.25-7.32 (m, 9H), 7.38-7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.86, 63.67, 85.84, 89.51, 122.55, 128.36, 128.52, 130.01, 131.70, 135.26; IR ($CHCl_3$) 3368, 3056, 2927, 2863, 2199, 1606, 1487 cm^{-1}; HRMS *m/z* 366.1616 (calcd for $C_{26}H_{22}O_2$, 366.1620).

1-Benzyl-3-phenylprop-2-ynyl acetate (58). To a solution of 1,4-diphenylbut-3-yn-2-ol (2 mmol) in 10 mL of CH_3CN was added acetic anhydride (2.2 mmol) and 4-

(dimethylamino)pyridine (2.2 mmol) at room temperature. The mixture was stirred at room temperature for 12 h. The mixture was quenched by the addition of satd aq NH_4Cl and extracted twice with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using 20:1 hexane/EtOAc to give compound **58** (97%) as light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 3H), 3.11-3.13 (d, J = 6.8 Hz, 2H), 7.20-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.07, 41.44, 65.19, 86.38, 122.35, 127.20, 128.46, 128.52, 128.85, 129.95, 131.96, 136.14, 169.87; IR ($CHCl_3$) 2930, 1721 cm^{-1}; HRMS *m/z* 294.1145 (calcd for $C_{18}H_{16}O_2$, 294.1150)

[(*1R, 2R*) and (*1S, 2R*)]-2-Phenyl-1-(phenylethynyl)cyclohexanol, (59) and (61). To a stirred solution of phenylacetylene (1.94 g, 19 mmol) and TMEDA (2.87 mL, 19 mmol) in THF was added dropwise a 2.5 M solution of *n*-BuLi (7.6 mL, 19 mmol) in hexane at -78 °C. After stirring was continued for 1 h at -78 °C, a solution of 2-phenylcyclohexanone (1.74 g, 10 mmol) in 10 mL of THF was added dropwise to this reaction mixture, and stirring was continued for an additional hour at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The residue upon work-up was chromatographed on silica gel using 20:1 hexane/EtOAc to afford compound **59** in a 38% yield as a sticky light yellow oil and compound **61** in a 32% yield as a yellow oil. Their structures were determined by NOESY NMR spectroscopy (see the spectra that follow) of the corresponding methyl ethers. **59**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35-1.45 (m, 1H), 1.58-1.96 (m, 6H), 2.05-2.20 (q, J = 13.0, 3.3 Hz, 1H), 2.25-2.30 (d, J = 13.0 Hz, 1H), 2.82-2.88 (dd, J = 13.0, 3.6 Hz, 1H), 7.17-7.32 (m, 8H), 7.37-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.19, 26.40, 26.98, 40.08, 53.13, 69.58, 85.01, 93.81, 123.21, 127.31, 128.23, 128.47, 128.50,

129.77, 131.89, 142.12; IR ($CHCl_3$) 3560, 3449, 3030, 2934 cm^{-1}; HRMS *m/z* 276.1519 (calcd for $C_{20}H_{20}O$, 276.1514). **61**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26-1.42 (m, 1H), 1.66-1.83 (m, 6H), 2.00-2.09 (m, 1H), 2.23-2.31 (m, 2H), 2.68-2.73 (dd, *J* = 13.0, 2.4 Hz, 1H), 7.21-7.33 (m, 7H), 7.37-7.43 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.62, 26.40, 30.40, 40.66, 55.52, 73.11, 87.71, 90.70, 123.26, 127.32, 128.31, 128.59, 128.61, 129.85, 131.89, 141.00; IR ($CHCl_3$) 3542, 2431, 3030, 2934, 2860 cm^{-1}; HRMS *m/z* 276.1519 (calcd for $C_{20}H_{20}O$, 276.1514).

[(*1R, 2R*) and (*1S, 2R*)]-2-Phenyl-1-(phenylethynyl)cyclohexyl methyl ether, (62) and (63). To a stirred solution of [(*1R*, *2R*) or (*1S*, *2R*)]-2-phenyl-1-(phenylethynyl)cyclohexanol (2 mmol) in THF was added NaH (60 % in mineral oil) (10 mmol). After stirring was continued for 10 min at room temperature, MeI (20 mmol) was added dropwise to this reaction mixture, and stirring was continued for an additional hour. The reaction mixture was diluted with water and extracted with Et_2O. The residue upon work-up was chromatographed on silica gel using 20:1 hexane/EtOAc to afford compound **62** in a 100% yield as a light yellow solid and compound **63** in an 80% yield as a colorless oil. **62**: mp 82-83 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.45 (m, 1H), 1.50-1.68 (m, 4H), 1.82-1.85 (m, 1H), 2.13-2.20 (m, 1H), 2.41-2.44 (d, *J* = 12.4 Hz, 1H), 2.81-2.85 (m, 1H), 3.30 (s, 3H), 7.19-7.29 (m, 8H), 7.40-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.70, 26.28, 27.76, 34.83, 51.14, 53.85, 75.15, 86.52, 90.82, 123.15, 126.44, 127.37, 128.10, 128.20. 129.93, 131.76, 142.95; IR ($CHCl_3$) 3034, 2938, 2856, 1487 cm^{-1}; HRMS *m/z* 290.1674 (calcd for $C_{22}H_{22}O$, 290.1671). **63**: 1.30-1.60 (m, 2H), 1.75-1.84 (m, 4H), 2.05-2.14 (m, 1H), 2.38-2.41 (d, *J* = 12.4 Hz, 1H), 2.76-2.80 (m, 1H), 3.23 (s, 3H), 7.17-7.30 (m, 6H), 7.42-7.45 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.07, 26.25, 31.00, 37.80, 51.66, 54.02,

78.75, 87.86, 89.70, 123.12, 126.53, 127.48, 128.30, 128.36, 129.52, 131.69, 142.44; IR ($CHCl_3$) 3033, 2935, 2855 cm^{-1}; HRMS *m/z* 290.1674 (calcd for $C_{22}H_{22}O$, 290.1671).

1,4-Diphenyl-3-butyn-2-one (64). To the solution of 1,4-diphenylbut-3-yn-2-ol (2.0 mmol) in 10 mL of CH_2Cl_2 was added Dess-Martin periodinane (2.4 mmol). The mixture was stirred for 2 h. The reaction was diluted with another 20 mL of CH_2Cl_2. The organic layer was washed with 20 mL of satd aq $Na_2S_2O_3$, 20 mL of satd aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using 10:1 hexane/EtOAc to afford compound **64** in an 80% yield as a light yellow oil. The spectral properties were identical with those previously reported.[30]

4-(Cyclohexen-1-yl)-1-phenylbut-3-yn-2-one (67). Compound **67** was prepared by the method used to prepare **64**, except that 4-(cyclohexen-1-yl)-1-phenylbut-3-yn-2-ol was used as the starting material. The residue was purified by column chromatography on silica gel using 10:1 hexane/EtOAc to afford compound **67** in a 58% yield as a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) 1.55-1.63 (m, 4H), 2.05-2.13 (m, 4H), 3.82 (s, 2H), 6.35-6.36 (m, 1H), 7.25-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.08, 21.92, 26.20, 28.19, 52.23, 86.19, 95.58, 118.97, 127.29, 128.67, 129.87, 133.55, 143.07, 185.45; IR ($CHCl_3$) 3031, 2937, 2865, 2186, 1712, 1671 cm^{-1}; HRMS *m/z* 224.1204 (calcd for $C_{16}H_{16}O$, 224.1201).

4-Cyclohexyl-1-phenylbut-3-yn-2-one (69). Compound **69** was prepared by the method used to prepare **64**, except that 4-cyclohexyl-1-phenylbut-3-yn-2-ol was used as the starting material. The reaction mixture was purified by column chromatography on silica gel using 10:1 hexane/EtOAc to afford compound **69** in an 83% yield as a light yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) 1.37-1.46 (m, 6H), 1.57-1.74 (m, 4H), 2.46-2.50 (m, 1H), 3.78 (s,

2H), 7.22-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.51, 25.65, 29.08, 31.45, 52.39, 80.72, 100.17, 127.28, 128.65, 129.87, 133.51, 185.58; IR ($CHCl_3$) 2938, 2860, 2233, 1695 cm^{-1}; HRMS *m/z* 226.1360 (calcd for $C_{16}H_{18}O$, 226.1358).

General Procedure for the Electrophilic Cyclization of Alkynols by I_2. 0.3 Mmol of the alkynol, 3 equiv of I_2, 2 equiv of $NaHCO_3$, and 3 mL of CH_3CN were placed in a vial. The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC to establish completion. The reaction mixture was diluted with 25 mL of ether, and washed with 20 mL of satd aq $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

General Procedure for the Electrophilic Cyclization of Alkynols by ICl, Br_2, and PhSeBr. 0.30 Mmol of the alkynol, 2 equiv of $NaHCO_3$ and 2 mL of CH_3CN were placed in a vial. 2 Equiv of ICl, Br_2, or PhSeBr in 1 mL of CH_3CN were added dropwise to the vial. The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was then diluted with 25 mL of ether, and washed with 20 mL of satd aq $Na_2S_2O_3$. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

General Procedure for the Electrophilic Cyclization of Alkynols by NBS. 0.30 Mmol of the alkynol, 1.5 equiv of NBS and 6 mL of CH_3CN were placed in a vial. The reaction mixture was reflux for 20 min under Ar. The reaction mixture was then diluted with

25 mL of ether, and washed with 20 mL of satd aq $Na_2S_2O_3$ The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

2-Iodo-1-phenylnaphthalene (2). The reaction mixture was chromatographed using hexane to afford 74 mg (75%) or 92 mg (93%) of the product as a colorless oil from I_2 or ICl, respectively. The spectral properties were identical with those previously reported.[19]

2-Bromo-1-phenylnaphthalene (3). The reaction mixture was chromatographed using hexane to afford 76 mg (89%) of the product as a colorless oil. The spectral properties were identical with those previously reported.[19]

1-Phenyl-2-(phenylseleno)naphthalene (4). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 39 mg (36%) of the product as a white solid: mp 93-94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.54 (m, 14H), 7.66-7.68 (d, J = 8.7 Hz, 1H), 7.80-7.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 125.76, 126.37, 126.72, 128.11, 128.13, 128.19, 128.39, 128.41, 128.75, 129.67, 130.44, 130.74, 131.26, 132.40, 133.34, 135.27, 139.89, 139.94; IR ($CHCl_3$) 3054, 1648, 1572 cm^{-1}; HRMS *m/z* 360.0422 (calcd for $C_{22}H_{16}Se$, 360.0417).

2-Iodo-1-(4-methoxyphenyl)naphthalene (6). The reaction mixture was chromatographed using 40:1 hexane/EtOAc to afford 81 mg (75%) of the product as a white solid: mp 110-111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H), 7.04-7.06 (m, 2H), 7.16-7.19 (m, 2H), 7.31-7.36 (m, 1H), 7.44-7.49 (m, 2H), 7.53-7.56 (d, J = 8.7 Hz, 1H), 7.81-7.84 (d, J = 8.4 Hz, 1H), 7.94-7.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.54, 99.50, 114.01, 126.40, 126.94, 127.52, 128.12, 129.14, 131.37, 133.13, 133.94, 135.72,

135.88, 144.45, 159.41; IR ($CHCl_3$) 3056, 2918, 2366, 1613 cm^{-1}; HRMS *m/z* 360.0017 (calcd for $C_{17}H_{13}IO$, 360.0011).

1-[4-(2-Iodo-1-naphthyl)phenyl]ethanone (8). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 64 mg (54%) or 109 mg (92%) of the product from I_2 or ICl respectively as a light yellow solid: mp 135-136 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.69 (s, 3H), 7.32-7.37 (m, 4H), 7.45-7.51 (m, 1H), 7.56-7.59 (d, *J* = 8.7 Hz, 1H), 7.82-7.85 (d, *J* = 8.1 Hz, 1H), 7.93-7.96 (d, *J* = 8.7 Hz, 1H), 8.10-8.13 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.03, 97.78, 126.68, 126.90, 127.29, 128.31, 128.82, 129.72, 130.70, 133.01, 133.18, 135.71, 136.75, 143.50, 148.28, 197.99; IR ($CHCl_3$) 3054, 2924, 2847, 1693 cm^{-1}; HRMS *m/z* 372.0017 (calcd for $C_{18}H_{13}IO$, 372.0011).

2-(2-Iodo-1-naphthyl)thiophene (10). The reaction mixture was chromatographed using hexane to afford 95 mg (94%) of the product as a colorless sticky oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.01-7.02 (m, 1H), 7.19-7.22 (m, 1H), 7.36-7.38 (m, 1H), 7.40-7.51 (m, 2H), 7.56-7.61 (m, 2H), 7.80-7.82 (d, *J* = 8.4 Hz, 1H), 7.93-7.95 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.61, 126.45, 126.50, 127.12, 127.21, 127.89, 128.57, 130.09, 132.71, 134.62, 135.46, 137.29, 143.89 (one carbon is missing due to overlap); IR ($CHCl_3$) 3106, 3066, 1643 cm^{-1}; HRMS *m/z* 335.9476 (calcd for $C_{14}H_9IS$, 335.9470).

2-(2-Bromo-1-naphthyl)thiophene (11). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 39 mg (45%) of the product as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.05-7.06 (m, 1H), 7.21-7.24 (m, 1H), 7.42-7.53 (m, 3H), 7.61-7.63 (d, *J* = 8.4 Hz, 1H), 7.70-7.76 (m, 2H), 7.83-7.85 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 124.08, 126.28, 126.54, 126.57, 127.05, 127.25, 127.92, 128.68,

129.87, 130.03, 132.21, 132.61, 135.04, 139.78; IR ($CHCl_3$) 3062, 2925, 2853, 1584 cm^{-1}; HRMS *m/z* 287.9612 (calcd for $C_{14}H_9BrS$, 287.9608).

5-Bromo-2-(2-bromo-1-naphthyl)thiophene (12). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 39 mg (36%) of the product as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.80-6.81 (d, *J* = 4.0 Hz, 1H), 7.15-7.16 (d, *J* = 3.6 Hz, 1H), 7.44-7.50 (m, 2H), 7.66-7.75 (m, 3H), 7.82-7.84 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.07, 124.14, 126.23, 126.43, 127.51, 128.03, 129.18, 129.85, 129.94, 130.48, 131.51, 132.20, 134.80, 141.40; IR ($CHCl_3$) 3053, 2924, 2853, 1582, 1503, 1442 cm^{-1}; HRMS *m/z* 367.8700 (calcd for $C_{14}H_8Br_2S$, 367.8693).

1-(Cyclohex-1-enyl)-2-iodonaphthalene (14). The reaction mixture was chromatographed using hexane to afford 69 mg (69%) of the product as a colorless sticky oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76-1.92 (m, 4H), 2.11-2.16 (m, 1H), 2.28-2.31 (m, 1H), 2.36-2.37 (m, 3H), 5.63-5.64 (m, 1H), 7.40-7.47 (m, 3H), 7.75-7.77 (m, 1H), 7.83-7.85 (d, *J* = 8.4 Hz, 1H), 7.91-7.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.19, 23.07, 25.48, 29.46, 97.47, 126.11, 126.63, 126.73, 128.07, 128.16, 128.81, 132.43, 133.05, 135.61, 140.42, 146.51; IR ($CHCl_3$) 3056, 2927, 2857, 2837, 1643 cm^{-1}; HRMS *m/z* 334.0222 (calcd for $C_{16}H_{15}I$, 334.0219).

1-Butyl-2-iodonaphthalene (16). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 70 mg (75%) of the product as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.00-1.04 (t, *J* = 7.2 Hz, 3H), 1.53-1.66 (m, 2H), 3.23-3.27 (t, *J* = 7.2 Hz, 3H), 7.37-7.39 (d, *J* = 8.8 Hz, 3H), 7.47-7.51 (m, 2H), 7.78-7.80 (m, 1H), 7.83-7.85 (d, *J* = 8.4 Hz, 1H), 8.03-8.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.05, 23.15, 31.88, 37.64,

99.35, 124.60, 125.95, 126.68, 127.82, 128.72, 132.17, 133.49, 136.34, 141.85; IR ($CHCl_3$) 3051, 2962, 2927, 2877, 1653 cm^{-1}; HRMS *m/z* 310.0220 (calcd for $C_{14}H_{15}I$, 310.0219).

1-Cyclohexyl-2-iodonaphthalene (18). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 91 mg (90%) of the product as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.57 (m, 3H), 1.84-1.95 (m, 5H), 2.23-2.33 (m, 2H), 3.60-3.66 (m, 1H), 7.30-7.32 (d, *J* = 8.4 Hz, 1H), 7.42-7.46 (m, 2H), 7.76-7.78 (m, 2H), 7.88-7.90 (d, *J* = 8.8 Hz, 1H), 8.42-8.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.28, 27.54, 31.10, 53.47, 101.43, 125.22, 125.65, 125.72, 128.31, 129.14, 131.86, 134.74, 137.00, 144.71; IR ($CHCl_3$) 3056, 2937, 2857, 1583 cm^{-1}; HRMS *m/z* 336.0380 (calcd for $C_{16}H_{17}I$, 336.0375).

1,2-Diiodonaphthalene (21). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 57 mg (50%) of the product as a white solid: mp 81-82 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49-7.57 (m, 3H), 7.70-7.72 (m, 1H), 7.89-7.92 (d, *J* = 8.8 Hz, 1H), 8.23-8.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.39, 113.68, 126.95, 128.52, 128.99, 130.00, 132.20, 135.36, 135.81, 136.89; IR ($CHCl_3$) 3086, 3039 cm^{-1}; HRMS *m/z* 379.8565 (calcd for $C_{10}H_6I_2$, 379.8559).

1-Ethoxy-2-iodonaphthalene (23). The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 46 mg (54%) of the product as a light yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57-1.61 (t, *J* = 7.2 Hz, 3H), 4.09-4.14 (q, *J* = 7.2 Hz, 2H), 7.34-7.36 (d, *J* = 8.8 Hz, 1H), 7.48-7.50 (m, 2H), 7.74-7.76 (d, *J* = 8.4 Hz, 1H), 7.79-7.81 (m, 1H), 8.06-8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.84, 70.28, 87.60, 122.35, 125.57, 126.55, 126.73, 128.03, 128.70, 134.76, 135.27, 155.71; IR ($CHCl_3$) 3057, 2978, 2928, 2885 cm^{-1}; HRMS *m/z* 297.9858 (calcd for $C_{12}H_{11}IO$, 297.9855).

2-Iodo-3,7-dimethyl-1-phenylnaphthalene (27). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 82 mg (78%) of the product as a light yellow solid: mp 78-79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H), 2.65 (s, 3H), 7.04 (s, 1H), 7.19-7.22 (m, 2H), 7.25-7.29 (d, J = 8.4 Hz, 1H), 7.48-7.52 (m, 3H), 7.63-7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.12, 30.42, 107.30, 126.36, 127.20, 127.21, 127.87, 128.64, 128.69, 128.87, 130.31, 131.52, 131.95, 135.84, 137.41, 144.98; IR ($CHCl_3$) 3050, 2947, 2919, 2855 cm^{-1}; HRMS *m/z* 358.0225 (calcd for $C_{18}H_{15}I$, 358.0219).

2-Iodo-4-methyl-1-phenylnaphthalene (29). The reaction mixture was chromatographed using hexane to afford 78 mg (76%) of the product as a white solid: mp 103-104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.68 (s, 3H), 7.22-7.25 (m, 2H), 7.33-7.35 (m, 1H), 7.40-7.54 (m, 5H), 7.85 (s, 1H), 7.96-7.99 (d, J = 8.4 Hz,1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.21, 98.59, 124.49, 126.22, 126.65, 127.99, 128.10, 128.61, 130.43, 132.32, 133.57, 135.86, 136.09, 143.11, 143.72; IR ($CHCl_3$) 3062, 3029, 2943, 2920, 2856, 1580 cm^{-1}; HRMS *m/z* 344.0068 (calcd for $C_{17}H_{13}I$, 344.0062).

2-Iodo-7-methoxy-1-phenylnaphthalene (31). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 97 mg (90%) of the product as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3H), 6.67 (s, 1H), 7.11-7.15 (d, J = 8.8 Hz, 2H), 7.25-7.27 (m, 2H), 7.47-7.52 (m, 4H), 7.72-7.74 (d, J = 9.2 Hz, 1H), 7.82-7.85 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.14, 99.19, 106.01, 118.62, 127.89, 128.43, 128.57, 128.70, 129.49, 129.95, 133.33, 134.61, 143.15, 143.53, 158.14; IR ($CHCl_3$) 3058, 2956, 2933, 2849,1622, 1500 cm^{-1}; HRMS *m/z* 360.0017 (calcd for $C_{17}H_{13}IO$, 360.0011).

2-Bromo-7-methoxy-1-phenylnaphthalene (32). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 86 mg (55%) of the product as a

colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3H), 6.69-6.70 (d, J = 2.4 Hz, 1H), 7.11-7.14 (dd, J = 2.4, 8.8 Hz, 1H), 7.29-7.31 (m, 2H), 7.45-7.53 (m, 3H), 7.56-7.64 (m, 2H), 7.72-7.74 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.15, 105.47, 118.40, 122.22, 127.65, 127.81, 127.89, 128.51, 128.66, 129.54, 130.07, 135.20, 138.56, 139.89, 158.28; IR ($CHCl_3$) 3058, 3001, 2959, 2937, 2838 cm^{-1}; HRMS *m/z* 312.0155 (calcd for $C_{17}H_{13}BrO$, 312.0150).

3-Hydroxy-2-iodo-1-phenylspiro[4.5]deca-1,6,9-trien-8-one (33). The reaction mixture was chromatographed using EtOAc to afford 27.3 mg (25%) of the product as a yellow solid: mp 168-170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32-2.36 (m, 1H), 2.61-2.67 (m, 2H), 5.02-5.04 (m, 1H), 6.21-6.26 (m, 2H), 6.76-6.79 (m, 1H), 6.95-6.98 (m, 1H), 7.12-7.13 (m, 2H), 7.26-7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.02, 56.87, 81.10, 106.18, 127.74, 128.32, 128.83, 129.15, 129.65, 134.94, 150.50, 151.31, 152.34, 185.39; IR (CH_2Cl_2) 3369, 1667, 1613 cm^{-1}; HRMS *m/z* 363.9968 (calcd for $C_{16}H_{13}IO_2$, 363.9960).

7-Fluoro-2-iodo-3-methyl-1-phenylnaphthalene (35). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 86 mg (79%) of the product as a light yellow solid: mp 112-114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (s, 3H), 6.89-6.94 (m, 1H), 7.19-7.24 (m, 3H), 7.48-7.55 (m, 3H), 7.72-7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.36, 108.41, 110.86, 111.16, 116.81, 117.15, 127.06, 127.07, 128.18, 128.86, 129.63, 129.75, 130.07, 130.23, 130.24, 132.34, 132.46, 137.79, 137.82, 144.31, 145.08, 159.07, 162.33 (the extra peaks are due to F splitting); IR ($CHCl_3$) 3056, 2921, 1628 cm^{-1}; HRMS *m/z* 361.9975 (calcd for $C_{17}H_{12}FI$, 361.9968); Anal. Calcd for $C_{17}H_{12}FI$: C, 56.4; H, 3.4; Found: C, 56.2; H, 3.9.

2-Iodo-1-phenylphenanthrene (37). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 83 mg (70%) of product as a white solid: mp 162-163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.40 (m, 3H), 7.52-7.70 (m, 6H), 7.85-7.88 (d, *J* = 8.1 Hz, 1H), 8.16-8.19 (d, *J* = 8.8 Hz, 1H), 8.43-8.46 (d, *J* = 8.9 Hz, 1H), 8.70-8.73 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 99.39, 122.94, 123.96, 125.76, 127.23, 127.34, 127.92, 128.09, 128.67, 128.78, 130.07, 130.25, 131.63, 131.99, 136.27, 143.81, 145.10 (one carbon was missing due to overlap); IR ($CHCl_3$) 3082, 3050, 2921, 2860 cm^{-1}; HRMS *m/z* 380.0068 (calcd for $C_{20}H_{13}I$, 380.0062).

2-Iodo-6-methoxy-3-methyl-1-phenylnaphthalene (39). The reaction mixture was chromatographed using 40:1 hexane/EtOAc to afford 93 mg (83%) of product as a sticky oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (s, 3H), 3.91 (s, 3H), 6.90-6.91 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.06-7.07 (d, *J* = 2.4 Hz, 1H), 7.19-7.23 (m, 3H), 7.47-7.52 (m, 3H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.25, 55.38, 103.46, 105.00, 118.45, 126.32, 127.23, 127.68, 128.41, 128.97, 130.00, 134.31, 138.80, 144.59, 145.28, 157.97 IR ($CHCl_3$) 2961, 2916, 2852, 1628 cm^{-1}; HRMS *m/z* 374.0174 (calcd for $C_{18}H_{15}IO$, 374.0168).

2-Iodo-6-methoxy-3-methyl-1-phenylnaphthalene (40). The reaction mixture was chromatographed using 40:1 hexane/EtOAc to afford 13.4 mg (12%) of product as a sticky oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (s, 3H), 3.91 (s, 3H), 6.90-6.91 (dd, *J* = 2.7, 9.3 Hz, 1H), 7.06-7.07 (d, *J* = 2.4 Hz, 1H), 7.19-7.23 (m, 3H), 7.47-7.52 (m, 3H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.1, 56.4, 91.8, 104.0, 120.0, 124.5, 126.8, 127.2, 127.4, 129.0, 134.0, 136.6, 138.4, 145.0, 154.2; IR ($CHCl_3$) 2971, 2918, 2852, 1642 cm^{-1}; HRMS *m/z* 374.0174 (calcd $C_{18}H_{15}IO$, 374.0168).

3-Iodo-4-phenylphenanthrene (42). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 85 mg (75 %) of product as a white solid: mp 155-156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10-7.13 (m, 1H), 7.28-7.31 (m, 2H), 7.40-7.45 (m, 2H), 7.57-7.60 (m, 4H), 7.70-7.83 (m, 3H), 8.19-8.22 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.92, 125.72, 126.52, 127.20, 128.22, 128.36, 128.68, 128.86, 129.60, 130.02, 130.15, 130.20, 130.38, 133.61, 133.71, 136.99, 143.86, 148.11; IR ($CHCl_3$) 3067, 3052, 2923 cm^{-1}; HRMS *m/z* 380.0068 (calcd for $C_{20}H_{13}I$, 380.0062).

3-Iodo-4-phenyldibenzo[*b*,*d*]thiophene (44). The reaction mixture was chromatographed using hexane to afford 96 mg (83%) of the product as a white solid: mp 116-117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.52 (m, 7H), 7.70-7.77 (m, 2H), 7.96-7.99 (d, J = 8.4 Hz, 1H), 8.08-8.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 96.84, 121.99, 122.10, 122.78, 124.88, 127.46, 128.90, 128.99, 129.37, 135.61, 135.65, 135.85, 140.30, 141.18, 141.35, 143.11; IR ($CHCl_3$) 3056, 2918, 2360, 2849, 1564 cm^{-1}; HRMS *m/z* 385.9632 (calcd for $C_{18}H_{11}IS$, 385.9626).

4-(Cyclohexen-1-yl)-3-iododibenzo[*b*,*d*]thiophene (46). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford 86 mg (74%) of product as a white solid: mp 105-106 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.75-1.92 (m, 4H), 2.25-2.28 (m, 3H), 2.39-2.44 (m, 1H), 5.78-5.81 (m, 1H), 7.38-7.47 (m, 2H), 7.65-7.67 (d, J = 8.1 Hz, 1H), 7.77-7.80 (m, 1H), 7.84-7.87 (d, J = 8.1 Hz, 1H), 8.05-8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.23, 23.13, 25.55, 27.76, 96.06, 121.22, 121.98, 122.81, 124.68, 127.28, 129.29, 135.25, 135.58, 135.89, 140.18, 140.51, 141.24, 143.33; IR ($CHCl_3$) 3062, 2933, 2834, 2853, 1432 cm^{-1}; HRMS *m/z* 389.9946 (calcd for $C_{18}H_{15}IS$, 389.9939); Anal. Calcd for $C_{18}H_{15}IS$: C, 55.4; H, 3.9; Found: C, 55.9; H, 4.4.

2-Iodo-3-methyl-1-phenyl-9*H*-carbazole (48). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 57 mg (50%) of the product as a white solid: mp 135-136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (s, 3H), 7.21-7.23 (d, J = 9.2 Hz, 1H), 7.26-7.28 (d, J = 8.0 Hz, 1H), 7.36-7.40 (m, 3H), 7.50-7.58 (m, 4H), 7.96 (s, 1H), 8.04-8.06 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.05, 103.04, 110.77, 119.65, 119.72, 120.60, 122.80, 123.04, 126.39, 128.35, 129.09, 130.02, 130.16, 132.37, 136.62, 139.60, 141.56; IR ($CHCl_3$) 3433, 3058, 2921, 2849 cm^{-1}; HRMS *m/z* 383.0177 (calcd for $C_{19}H_{14}IN$, 383.0171).

2-Iodo-1-phenyl-3,4-dihydronaphthalene (50). The reaction mixture was chromatographed using hexane to afford 76 mg (76%) of the product as a white solid: mp 80-81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95-2.99 (m, 2H), 3.07-3.11 (m, 2H), 6.61-6.63 (d, J = 7.6 Hz, 1H), 6.99-7.03 (m, 1H), 7.13-7.19 (m, 4H), 7.38-7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.14, 39.80, 101.13, 126.39, 126.59, 127.39, 127.44, 127.61, 128.51, 129.67, 134.68, 135.25, 143.35, 144.56; IR ($CHCl_3$) 3062, 3017, 2940, 2889, 2832, 2361 cm^{-1}; HRMS *m/z* 332.0079 (calcd for $C_{16}H_{13}I$, 332.0062).

2,6-Diiodo-1,5-diphenylanthracene (56). The reaction mixture was chromatographed using hexane to afford 56 mg (32%) of the product as a white solid: mp 212-213 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.18 (m, 2H), 6.70 (m, 1H), 6.97-7.05 (m, 2H), 7.18-7.24 (m, 1H), 7.32-7.34 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 8.08-8.10 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 100.98, 126.92, 127.33, 127.62, 130.82, 134.99, 139.62, 142.43, 144.67; IR ($CHCl_3$) 3080, 3052, 3031, 2919, 2850 cm^{-1}; HRMS *m/z* 581.9344 (calcd for $C_{26}H_{16}I_2$, 581.9341); Anal. Calcd for $C_{26}H_{16}I_2$: C, 53.6; H, 2.8; Found: C, 54.0; H, 3.1.

3,6-Diiodo-4,5-diphenylphenanthrene (57). The reaction mixture was chromatographed using hexane to afford 35 mg (20%) of the product as a white solid: decomposes at 195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.24 (m, 2H), 7.26-7.30 (m, 3H), 7.39-7.41 (d, J = 9.2 Hz, 1H), 7.50-7.59 (m, 9H), 8.20-8.22 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 8.08-8.10 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 99.64, 104.26, 126.95, 127.77, 127.93, 128.25, 128.53, 129.17, 129.60, 129.81, 129.91, 129.97, 130.11, 132.82, 133.35, 134.73, 137.43, 143.76, 143.90, 144.29, 147.80; IR ($CHCl_3$) 3058, 2925, 2849 cm^{-1}; HRMS *m/z* 581.9344 (calcd for $C_{26}H_{16}I_2$, 581.9341).

10-Iodo-9-phenyl-1,2,3,4-tetrahydrophenanthrene (60). The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford the product as a light yellow solid (72% from **59**, 99% from **61**): mp 134-135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92-1.93 (m, 4H), 2.91-2.94 (m, 2H), 3.18-3.21 (m, 2H), 7.21-7.33 (m, 4H), 7.46-7.53 (m, 4H), 8.01-8.03 (d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.90, 24.25, 27.02, 38.62, 109.99, 122.87, 125.58, 126.24, 127.60, 128.15, 128.43, 130.27, 131.90, 132.03, 133.59, 135.65, 143.70 145.27; IR ($CHCl_3$) 3067, 2930, 2856 cm^{-1}; HRMS *m/z* 384.0380 (calcd for $C_{20}H_{17}I$, 384.0375).

3-Iodo-4-phenyl-2-naphthol (65). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford the product as a light yellow solid: mp 65-68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.68 (s, 1H), 7.17-7.19 (m, 1H), 7.22-7.25 (m, 2H), 7.28-7.30 (d, J = 8.8 Hz, 1H), 7.41-7.53 (m, 5H), 7.72-7.74 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.82, 109.00, 124.34, 126.60, 127.12, 127.31, 128.10, 128.61, 128.71, 129.81, 134.64, 143.40, 146.44, 151.08; IR ($CHCl_3$) 3435, 3061, 1648 cm^{-1}; HRMS *m/z* 345.9860 (calcd for $C_{16}H_{11}IO$, 345.9855).

4-(Cyclohexen-1-yl)-3-iodo-2-naphthol (68). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 68 mg (65%) of the product as a light orange oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77-1.93 (m, 4H), 2.15-2.18 (m, 1H), 2.29-2.32 (m, 3H), 5.63-5.65 (m, 2H), 7.26-7.30 (m, 2H), 7.40-7.44 (m, 1H), 7.66-7.68 (d, J = 8.0 Hz, 1H), 7.81-7.83 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.11, 23.03, 25.43, 29.31, 95.64, 108.11, 124.20, 126.74, 126.76, 126.99, 127.52, 129.4, 134.76, 140.59, 148.48, 151.14; IR ($CHCl_3$) 3470, 3058, 2928, 2856, 2834, 1563 cm^{-1}; HRMS *m/z* 350.0172 (calcd for $C_{16}H_{15}IO$, 350.0168).

4-Cyclohexyl-3-iodo-2-naphthol (70). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 83 mg (79%) of the product as a light yellow solid: mp 103-104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44-1.56 (m, 3H), 1.84-1.97 (m, 5H), 2.26-2.35 (m, 3H), 3.66-3.72 (m, 1H), 5.72 (s, 1H), 7.24-7.31 (m, 2H), 7.37-7.41 (m, 1H), 7.66-7.68 (d, J = 8.0 Hz, 1H), 8.37-8.39 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.19, 27.55, 31.07, 54.52, 99.88, 108.70, 122.90, 125.53, 126.37, 126.82, 127.69, 135.37, 146.83, 150.96; IR ($CHCl_3$) 3463, 2941, 2925, 2853 cm^{-1}; HRMS *m/z* 352.0329 (calcd for $C_{16}H_{17}IO$, 352.0324).

8-Methoxyfluoranthene (71). To a solution of 2-iodo-1-(4-methoxyphenyl)naphthalene (0.20 mmol) and cesium pivalate (0.40 mmol) in 3.5 mL of DMF were added $Pd(OAc)_2$ (2.5 mg, 5 mol %) and DPPM (3.84 mg, 10 mol %). The resulting mixture was heated under an N_2 atmosphere at 120 °C for 24 h. The mixture was cooled to room temperature and diluted with 25 ml of ether, washed with 25 mL of satd aq NaCl, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed using 40:1 hexane/EtOAc to afford 30.2 mg

(65%) of the product as a light yellow solid: mp 120-121 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.93 (s, 3H), 6.89-6.92 (m, 1H), 7.45-7.46 (m, 1H), 7.56-7.63 (m, 2H), 7.74-7.84 (m, 4H), 7.89-7.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 55.89, 107.93, 113.08, 119.23, 120.20, 122.47, 125.71, 127.15, 128.01, 128.30, 130.19, 132.69, 133.11, 137.08, 137.22, 141.50, 160.20; IR ($CHCl_3$) 3053, 3012, 2971, 2940, 2832, 2361, 1603 cm^{-1}; HRMS *m/z* 232.0891 (calcd for $C_{17}H_{12}O$, 232.0888).

1-(Fluoranthen-8-yl)ethanone (71). To a solution of 1-[4-(2-iodo-1-naphthyl)phenyl]ethanone (0.20 mmol) and cesium pivalate (0.40 mmol, 2.0 equiv) in 3.5 mL of DMF were added $Pd(OAc)_2$ (2.5 mg, 5 mol %) and DPPM (3.84 mg, 10 mol %). The resulting mixture was heated under an N_2 atmosphere at 120 °C for 3.5 d. The mixture was cooled to room temperature and diluted with 25 ml of ether, washed with 25 mL of satd aq NaCl, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed using 20:1 hexane/EtOAc to afford 31.2 mg (64%) of the product as a light green yellow solid: mp 95-96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70 (s, 3H), 7.64-7.69 (m, 2H), 7.87-8.01 (m, 6H), 8.47-8.48 (m, 1H), 7.74-7.84 (m, 4H), 7.89-7.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 27.11, 121.04, 121.44, 121.70, 127.45, 128.14, 128.33, 128.47, 128.55, 130.24, 133.37, 135.91, 136.23, 136.48, 139.83, 143.86, 198.19; IR ($CHCl_3$) 3050, 3005, 2925, 1678, 1614, 1432 cm^{-1}; HRMS *m/z* 244.0892 (calcd for $C_{18}H_{12}O$, 244.0888).

2,4-Diphenylnaphtho[2,3-*b*]furan (73). To a solution of 3-iodo-4-phenyl-2-naphthol (0.42 mmol) in 4 mL of NEt_3/DMF (V/V = 1/1) in a vial was added $PdCl_2(PPh_3)_2$ (15 mg, 2.5 mol %), CuI (2.1 mg, 1.25 mol %), and phenylacetylene (0.50 mmol, 1.2 equiv). The vial was flushed with N_2 and sealed. The reaction mixture was heated to 100 °C for 12

h, cooled to room temperature, filtered, diluted with 25 ml of ether, washed with 25 mL of satd aq NaCl, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed using hexane to afford 67 mg (51%) of the product as a white solid: mp 183-184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (s, 1H), 7.23-7.37 (m, 2H), 7.42-7.45 (m, 3H), 7.49-7.52 (m, 1H), 7.55-7.58 (m, 1H), 7.87-7.98 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) 100.79, 106.36, 124.25, 124.81, 125.33, 125.86, 127.60, 128.29, 128.60, 128.63, 128.86, 129.12, 129.88, 130.17, 130.72, 131.22, 132.04, 138.28, 153.24, 158.17; IR ($CHCl_3$) 2924, 2852 cm^{-1}; HRMS *m/z* 320.1205 (calcd for $C_{24}H_{16}O$, 320.1201).

Acknowledgement. We gratefully acknowledge the National Institute of General Medical Sciences (GM 070620) for support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. for donations of palladium acetate.

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Chapter 4. Synthesis of Spirotrienones by Intramolecular *Ipso*-Halocyclization of 4-(*p*-Methoxyaryl)-1-alkynes

Based on a paper to be submitted to the *Journal of Organic Chemistry*

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Abstract

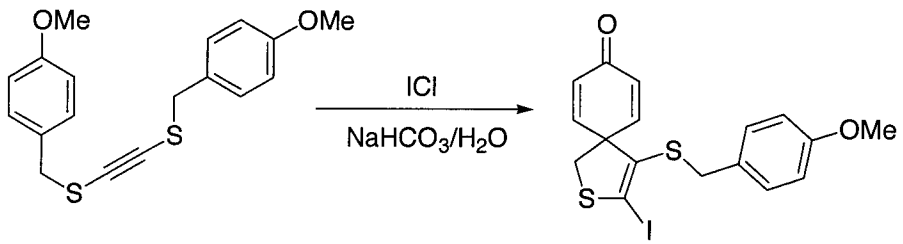
The electrophile-induced intramolecular *ipso*-cyclization of 4-(*p*-methoxyaryl)-1-alkynes provides an efficient approach to various halogen-substituted spirotrienones. ICl, I_2 and Br_2 are all effective electrophiles for this process. The reaction is very general, and a wide variety of functional groups can be tolerated under the very mild reaction conditions.

Introduction

Intramolecular hydroarylation, a formal addition of arene C-H bonds across multiple bonds in an intramolecular manner, provides a direct route to valuable organic compounds, such as annulated heteroarenes and carbocycles.[1] Recently, considerable effort in this area has focused on the search for new processes involving reactive organometallic species.[2] Halonium ions promote such aromatic cyclizations. In the process, they not only rapidly construct the cyclic skeletons, but also generate more highly functionalized molecules. It has been demonstrated that the halogen-promoted cyclization of alkynes can be effectively employed in the synthesis of substituted dihydronaphthalenes,[3] chromenes,[4]

tetrahydroquinolines,[4] 1*H*-2-benzothiopyrans,[5] quinolines,[6] and polycyclic aromatic compounds.[7] This area continues to be particularly active.

The spiro[4.5]decane ring system is a key structural feature possessed by a number of sesquiterpenes, including the spirovetivanes, acorones, and alaskanes.[8] Many of these substances are phytoalexins, defensive chemical agents produced by plants in response to an infecting organism.[9] Spiro[4.5]decatrienones have been prepared by the intra-/inter-molecular reaction of 4-methoxyarenes with alkynes in the presence of Lewis acids[10] and the transition metal-mediated cyclization of alkoxy-substituted allenyl benzyl ketones.[11] The 1-azaspiro[4.5]decane skeleton is also a key structural unit possessed by a number of interesting natural products, such as TAN1251A-D,[12] FR901483,[13] lepadiformine,[14] and cyclindricine.[15] Construction of the 1-azaspiro[4.5]decane skeleton has been achieved by oxidative spirocyclization of *N*-methoxy-*N*-(4-methoxyphenyl)amides[16] or *N*-methoxy-*N*-(4-halophenyl)amides[17] via *N*-acyl-*N*-methoxynitrenium ion intermediates using hypervalent iodine reagents. Fanghänel *et al* have reported a single example of the iodo-spirocyclization of *bis*(4-methoxybenzylthio)acetylene (eq 1).[18] Unfortunately, this is the only substrate that has been investigated and the scope of this cyclization has not yet been examined.

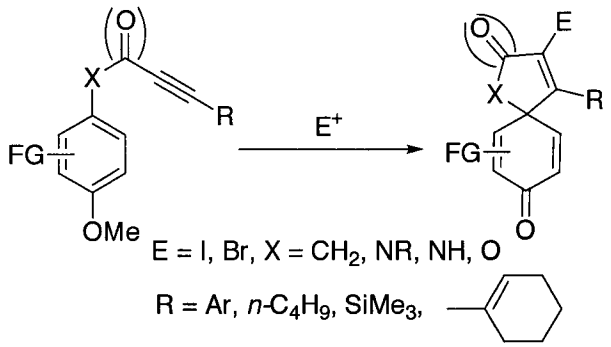


(1)

Herein, we wish to report the full details[19] of the successful electrophilic cyclization of a wide variety of 4-(4-methoxyaryl)-1-alkynes for the synthesis of halogen-substituted spirotrienones. The key step is the intramolecular *ispo* cyclization of a carbon-tethered or

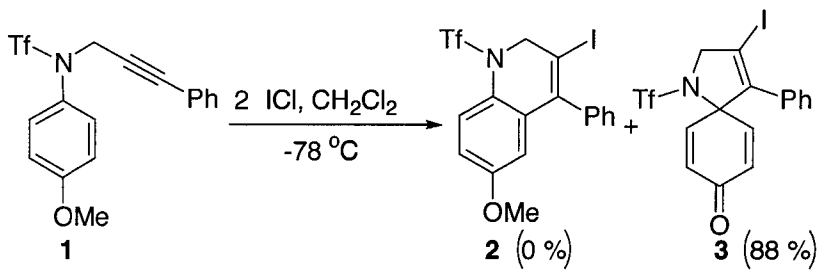
heteroatom-linked alkyne promoted by halogen reagents. This chemistry generally produces moderate to excellent yields of the desired products. ICl, I_2 and Br_2 can be used as electrophiles under different reaction conditions (Scheme 1).

Scheme 1



Results and Discussion

We initiated our study by treating *N*-(4-methoxyphenyl)-*N*-(3-phenyl-2-propyn-1-yl)triflamide (**1**) with 2 equiv of ICl in CH_2Cl_2 at -78 °C for 10 min (Conditions A). We anticipated that alkyne **1** might undergo *ortho* aromatic cyclization to give dihydroquinoline **2** (eq 2). However, none of the anticipated dihydroquinoline derivative



(2)

was observed. The 1-azaspirotrienone **3** was produced exclusively in an 88% yield (eq 2). When the reaction was carried out at r.t., the spirotrienone **3** was obtained in only a 46% yield together with a 48% yield of **2**. This indicates that *ipso*-cyclization is a kinetically favored process. This spirocyclization process has proven to be quite general (Table 1). The

yield of spirocyclic products is strongly dependent on the protecting group present on the nitrogen. The *N*-acetyl-protected amide **23** cyclized efficiently to generate spirocyclic product **24** in a 66% yield (entry 18, Table 1). However, the free aniline **50** reacted with ICl under the same reaction conditions to afford 3-iodo-6-methoxy-4-phenylquinoline as the only product in a 45% yield (entry 36). The corresponding *N*-methyl-protected aniline didn't generate *ipso*-attack product either. Obviously, electron-releasing protecting groups on the nitrogen facilitate *ortho* electrophilic aromatic substitution.

ICl is an efficient and quite general electrophile for this process. Most of the functional groups present in the substrates being studied readily tolerate the reaction conditions and good yields have been obtained (entries 1, 4, 7, 10, 12, 15 and 18). Both electron-rich and electron-poor aryl-substituted alkynes (entries 1, 4 and 7) and an alkyl-substituted alkyne (entry 10) are readily accommodated. The presence of a silyl group (entry 12) or an olefin (entry 15) on the acetylene terminus presents no difficulties. However, alkynes bearing a H or a *t*-butyl group on the remote end of the alkyne didn't afford the anticipated spirotrienone products (entries 13 and 14). In the former example, coordination of the iodine to the carbon-carbon triple bond as a bridged iodonium intermediate should result in a partial positive charge on the carbon next to the methylene group due to the hydrogen's inability to stablize a vinylic cation intermediate. Obviously, the formation of a 5-membered ring from such an intermediate is disfavored. On the other hand, the presence of a bulky *t*-butyl group also prevented electrophilic attack of the "vinylic cation" on the phenyl group and the starting alkyne was recovered after the reaction.

Table 1. Synthesis of Spirotrienones by the Reaction of Arylalkynes and Halogen Electrophiles[a]

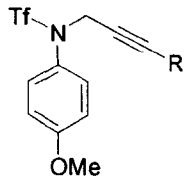
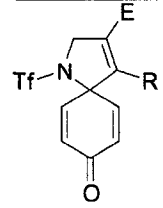
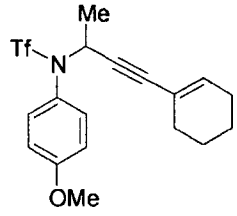
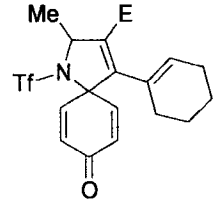
entry	arylalkyne		electrophile	cond.[a]	time (min)	product(s)			% yield
								E	
1	R = Ph	**1**	ICl	A	30		**3**	I	88
2			I_2	B	120				90
3			Br_2	B	10		**4**	Br	92
4	R = *p*-$MeOC_6H_4$	**5**	ICl	A	10		**6**	I	84
5			I_2	B	120				80
6			Br_2	B	10		**7**	Br	95
7	R = *p*-$MeCOC_6H_4$	**8**	ICl	A	30		**9**	I	89
8			I_2	B	120				48[b]
9			Br_2	B	10		**10**	Br	30
10	R = *n*-Bu	**11**	ICl	A	10		**12**	I	75
11			Br_2	B	10		**13**	Br	31
12	R = $SiMe_3$	**14**	ICl	A	30		**15**	I	58[c]
13	R = H	**16**	ICl	A	30		**17**	I	0
14	R = *t*-Bu	**18**	ICl	A	30		**19**	I	0
15		**20**	ICl	A	10		**21**	I	83
16			I_2	B	60				72
17			Br_2	B	10		**22**	Br	67

Table 1. Continued

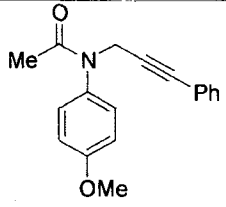
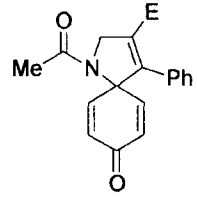
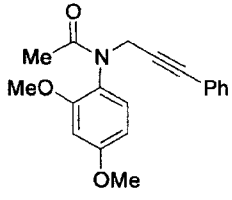
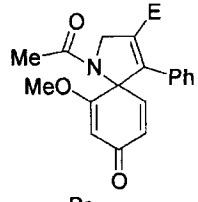
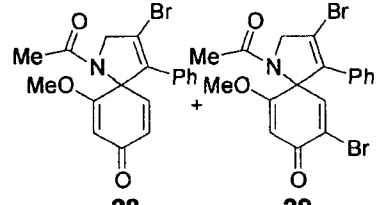
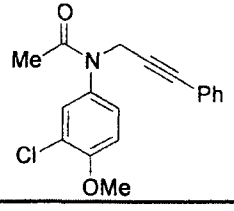
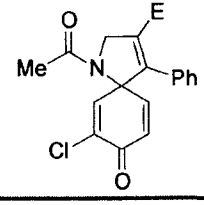
entry	arylalkyne		electrophile	cond.[a]	time (min)	product(s)			% yield
18		**23**	ICl	A	10		**24**	I	66[d]
19			Br_2	B	10		**25**	Br	60
20		**26**	ICl	A	10		**27**	I	72
21			Br_2	B	10	 **28** + **29**			54 + 45[e]
22		**30**	ICl	A	10		**31**	I	60

Table 1. Continued

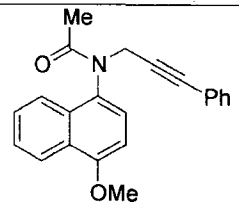
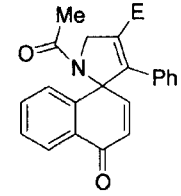
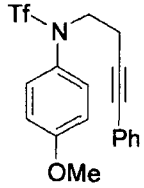
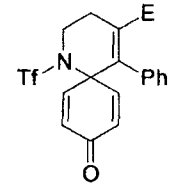
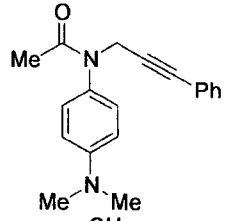
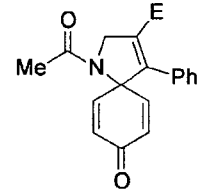
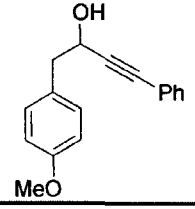
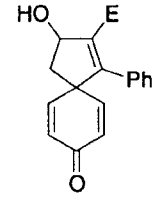
entry	arylalkyne		electrophile	cond.[a]	time (min)	product(s)		% yield
23		**32**	ICl	A	10		**33**	I	80
24			I_2	B	120				70
25			Br_2	B	10		**34**	Br	82
26		**35**	ICl	A	10		**36**	I	32[f]
27		**37**	ICl	A	10		**24**	I	61[d,g]
28		**38**	I_2	B	120		**39**	I	20

Table 1. Continued

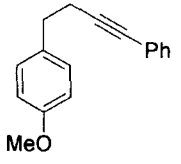
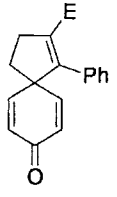
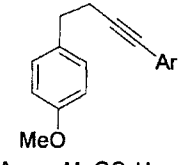
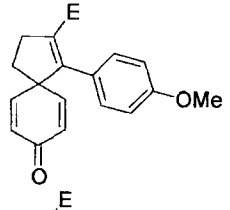
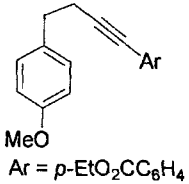
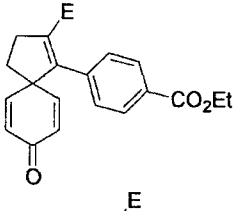
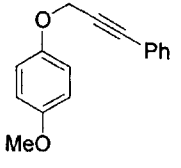
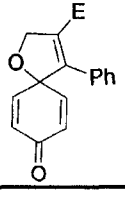
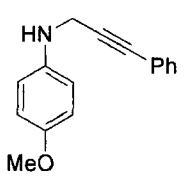
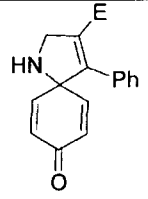
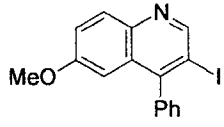
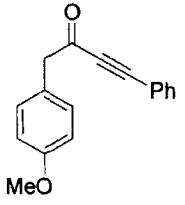
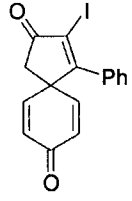
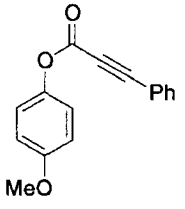
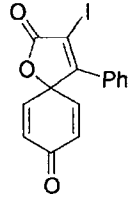
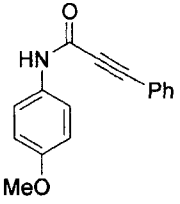
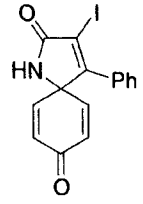
entry	arylalkyne		electrophile	cond.[a]	time (min)	product(s)			% yield
29			ICl	C	10			I	87
30			Br_2	B	10		**40**	Br	50
31		**41**	ICl	C	10		**42**	I	93
32			Br_2	C	10		**43**	Br	98
33	 Ar = *p*-$MeOC_6H_4$	**44**	ICl	C	10		**45**	I	92
34	 Ar = *p*-$EtO_2CC_6H_4$	**46**	Br_2	C	10		**47**	Br	36
35		**48**	Br_2	C	10		**49**	Br	0

Table 1. Continued

entry	arylalkyne		electrophile	cond.[a]	time (min)	product(s)		% yield
36		**50**	Br_2	C	10		**51** Br	0
37			ICl	A	30		**52**	45
38		**53**	ICl	A	10		**54** I	65
39			ICl	D[h]	10			92
40			I_2[i]	B	10			98
41		**55**	ICl	D[j]	10		**56** I	100
42			I_2	B	60		**56**	100

43		**57**	ICl	D	10		**58**	I	89
44			I_2	B[k]	120				84

[a] See the text for reaction conditions A-C. [b] After 3 days, 49% of **7** remained unreacted. [c] 3 Equiv of ICl were used. [d] 4 Equiv of ICl were used. [e] 3 Equiv of Br_2 were used. [fg] The product was obtained after acidic work-up. [h] Conditions D: the substrate was treated with 1.5 equiv of ICl in MeCN at r.t. for 5 min. [i] The reaction only took 10 min. [j] Under Conditions A, only a trace of the spirocycle was generated. [k] The reaction took 12 h.

1-Azaspirotrienones bearing electron-donating or electron-withdrawing substituents on the 6- or 7-positions of the spirodecatrienone skeleton respectively have also been synthesized in excellent yields (entries 20 and 22). This cyclization can also be applied to the naphthanilide system as a synthetically useful method to generate annulated spirotrienones in a good yield (entry 32,). The synthesis of 4-iodospirotrienones which have an interesting 1-azaspiro[5.5]undecane skeleton by the same strategy afforded a lower 32% yield of 6-*endo*-dig product **36**, together with a 40% yield of a chloroiodoalkene formed by simple ICl addition to the carbon-carbon triple bond (entry 26). No 5-*exo*-dig product was observed. Therefore, iodonium-promoted 6-*endo*-dig *ipso* cyclization must be slower than 5-*endo*-dig cyclization, since the former leads to quenching of the vinylic cation by Cl^-, instead of intramolecular quenching by the aromatic ring.

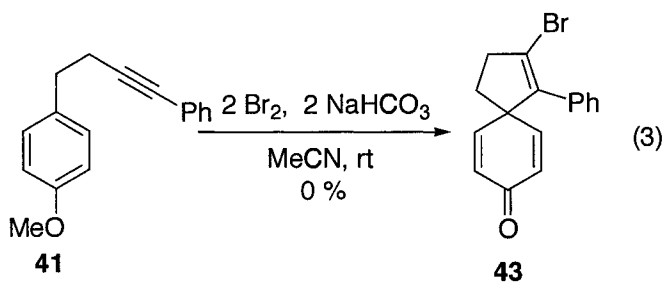
N-(4-Dimethylaminophenyl)anilides also undergo this *ipso* cyclization (entry 27). The corresponding spirotrienone was obtained in a high yield after acidic hydrolysis. Kikugawa *et al* reported that *N*-methoxy-*N*-(4-halophenyl)amides can be used as an alternative starting material to *N*-methoxy-*N*-(4-methoxyphenyl)amides in their oxidative spirocyclization.[17] Kikugawa also employed *N*-(4-fluorophenyl)anilides as starting materials, but *N*-(4-fluorophenyl)anilides didn't generate spirocyclic products in our iodocyclization process. PhSeCl, which has been successfully used in a number of our previous electrophilic *ortho*-aromatic substitution reactions,[6,7] failed to generate spirocyclization products when using alkyne **1** as the starting material.

The reagents I_2 and Br_2 have also been successfully employed as electrophiles in this spirotrienone synthesis. When **1** was treated with 2 equiv of I_2 and 2 equiv of $NaHCO_3$ in MeCN at r.t. for 1 h (Conditions B), the desired spirotrienone could be formed in a 90%

yield, although a longer reaction time was required compared with ICl (entries 1 and 2). Interestingly, simple removal of the base $NaHCO_3$ resulted in the formation of dihydroquinoline **2** as the sole product in an 80% yield by *ortho*-aromatic cyclization. It is important to note at this point that by modifying the reaction conditions, we can switch the *ipso*/*ortho* cyclizations "on" or "off" completely. The base may be preventing the proton-catalyzed rearrangement of the 5-membered ring *spiro* product to the six-membered ring dihydroquinoline (see the cyclohexadienone/phenol rearrangement[21]).

The choice of electrophilie is very important. In general, cyclizations employing I_2 work as well as ICl for phenyl-, electron-rich aryl-, and vinylic-substituted alkynes (entries 2, 5, 14, and 22). However, one reaction employing I_2 gave inferior results for an electron-poor aryl alkyne and a much longer reaction time was required (entry 8, Table 1). In contrast to I_2, the reactions with Br_2 under Conditions B are usually more general in terms of the alkyne substituents that work well. Moderate to good yields of products have been obtained and the reactions generally proceed faster (10 minutes *vs* 1 h) (entries 3, 6, 9, 11, 17, 19 and 21). We were pleased to find that a double bond on the alkyne terminus can survive the bromination reaction conditions and a monobromo-substituted 1-azaspirotrienone could be obtained in good yield (entry 17). When an *N*-(2,4-dimethoxyphenyl)anilide was used as the starting material, both 3-bromo- and 3,7-dibromospirotrienones were obtained in an overall 99% yield (entry 21). During the early work on optimization of the reaction conditions employing Br_2 as an electrophile, **1** was treated with 2 equiv of Br_2 in MeCN in the absence of base and a 20% yield of 3-bromospirotrienone **4** was obtained. This observation further proves that the formation of spiro compounds is under kinetic control, since the stronger electrophile (ICl over Br_2 over I_2) generates more *ipso* products.

When the reaction Conditions B were employed for the cyclization of **41**, none of the desired spirotrienone **43** was obtained (eq 3). On the other hand, compound **38** bearing hydroxyl functionality produced a 50% yield of the anticipated 3-bromospirotrienone under the same reaction conditions (entry 30). It was subsequently found that a small amount of the desired spiro product **43** could be obtained from **41** simply by using methanol as a co-solvent (entry 2, Table 2). This might be the result of the reduced nucleophilicity of the Br^- in methanol due to strong hydrogen bonding. Thus, the vinylic cation can attack intramolecularly diminishing the formation of side products, like dibromoalkenes, which are formed to a significant extent in the absence of a protic solvent. A stronger base, such as NaOMe, which has better solubility in this solvent system, is required for the success of this reaction as shown in entry 4, Table 2. An almost quantitative yield of the desired spirocyclic product can be obtained when the reaction was performed at a low temperature (compare entries 4 and 5, Table 2).



41 **43** (3)

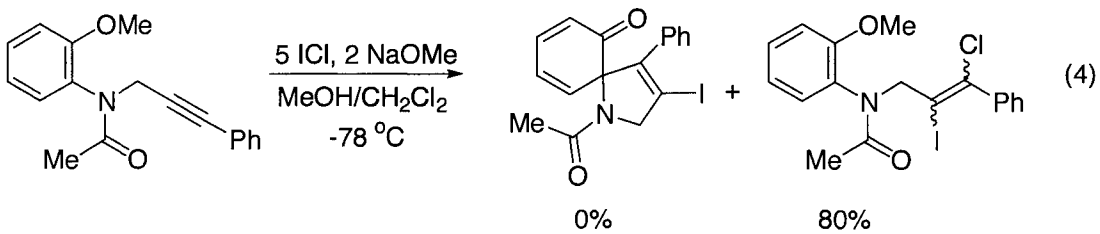
Table 2. Synthesis of Spirotrienones by Br_2 Cyclization (eq 3)

entry	2 equiv base	solvent	temp. (°C)	equiv of Br_2	% yield of **43**
1	$NaHCO_3$	MeCN	r.t.	2	0[a]
2	$NaHCO_3$	MeCN/MeOH[b]	r.t.	2	25
3	$NaHCO_3$	CH_2Cl_2/MeOH[c]	-78	2	40
4	**NaOMe**	**CH_2Cl_2/MeOH[c]**	**-78**	**5**	**98[d]**
5	NaOMe	CH_2Cl_2/MeOH[c]	r.t.	5	78

[a] Conditions B. [b] For 0.2 mmol of **41**, 4 mL of MeCN and 1 mL of MeOH were used. [c] For 0.3 mmol of **43**, 3 mL of CH_2Cl_2 and 4 mL of MeOH were used. [d] Conditions C. The reaction was complete in 10 min.

ICl also successfully promotes the cyclization under these reaction conditions (Conditions C). Simple phenyl- and 4-methoxyphenyl-substituted alkynes give excellent yields (entries 31 and 33, Table 1). A hydroxy moiety can also be readily accommodated under the reaction conditions C when using ICl (entry 29, Table 1). However, the yield dropped significantly when an aryl acetylene bearing an electron-withdrawing group was allowed to react with Br_2 under these carefully optimized reaction conditions (entry 34, Table 1). Unfortunately, all attempts to obtain an N-H-1-azaspirotrienone or a 1-oxospirotrienone have been unsuccessful under all reaction conditions so far studied (entries 35 and 36, Table 1). This is probably due to the electron-donating nature of the free amine and oxygen through resonance, which makes *ortho* substitution more favorable.

Despite the success of this methodology for preparing spiro-8-ones, we have so far been unable to obtain spiro-6-ones from the corresponding *N*-(2-methoxyphenyl)anilides using ICl and either Conditions A or C (eq 4). Similarly, none of spirotrien-6-one products were observed in the reactions described in entries 20 and 21 in Table 1.



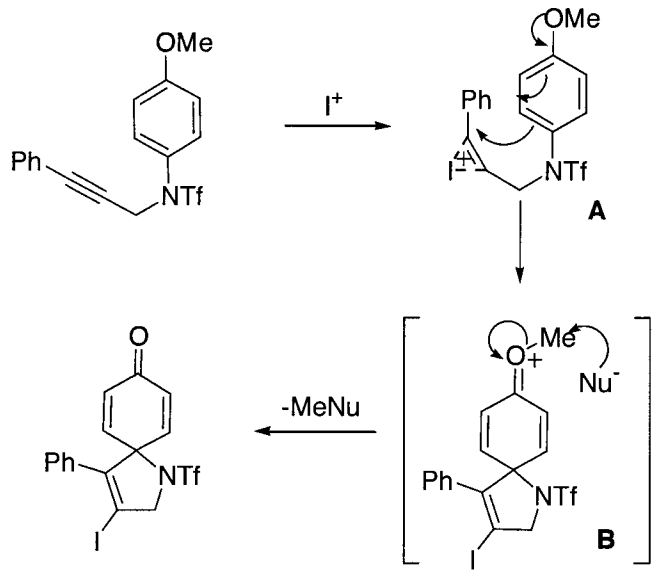
0% 80% (4)

This methodology has great synthetic potential considering the success we have had with a variety of linkages between the carbon-carbon triple bond and the methoxy-substituted arene. Thus, alkynone **53** cyclized smoothly using ICl as the electrophile under Conditions D

(MeCN as the solvent at r.t.) (entry 38, Table 1). A better yield was obtained using MeCN as the solvent, rather than CH_2Cl_2 (compare entries 38 and 39, Table 1). Similarly, employing ester and amide linkages has resulted in generation of the corresponding spiro compounds in excellent yields under Conditions D (entries 41 and 43, Table 1). Excellent yields can also be obtained using I_2 as the electrophile under Conditions B (entries 40, 42 and 44, Table 1). The reaction with a ketone linkage (entry 40, Table 1) was substantially faster than reaction of the corresponding amide (entry 44, Table 1) (10 min *vs* 12 h).

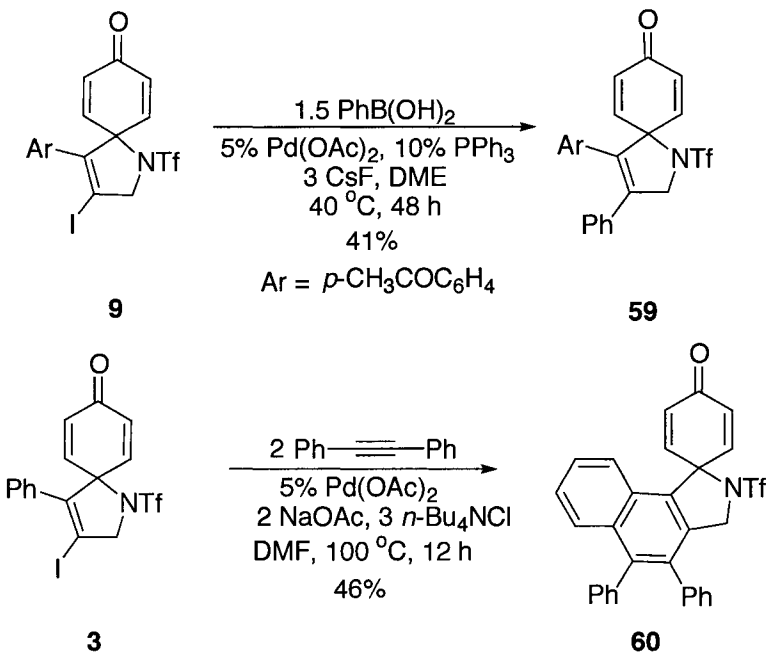
Based on the above observations, we propose the following mechanism (Scheme 2). Presumably these cyclizations proceed by coordination of the iodine or bromine cation to the carbon-carbon triple bond to generate an iodonium (bromonium) intermediate **A**, which undergoes intramolecular *ipso*-attack on the electron-rich aromatic ring to form intermediate **B**. The methyl group of **B** is then removed via nucleophilic displacement by the Cl^- (Conditions A and D), I^- or Br^- (Conditions B), or MeO^- (Conditions C) present in the reaction mixture.

Scheme 2



The synthetic potential of our 3-iodospirotrienones is high, particularly when one considers that further functional group manipulation of the halogen should allow the facile preparation of more highly-substituted spirotrienones. For example, the 3-iodospirotrienones produced by this strategy can be further functionalized by palladium-catalyzed reactions, such as a Suzuki cross-coupling process[22] or palladium-catalyzed carboannulation[23] to quickly achieve molecular complexity (Scheme 3).

Scheme 3



Conclusions

In conclusion, we have developed a new approach to various 3-halogen-substituted spirotrienones bearing the [4.5]decane and [5.5]undecane ring systems under mild reaction conditions through a process which readily tolerates considerable functionality. This process has been successful on a wide variety of acetylenes bearing a wide range of substituents on the remote end of the alkyne triple bond. ICl in the absence of base readily affords 1-

azaspirotrienones. A base is required for electrophilic *ipso*-cyclization using I_2 and Br_2. However, the formation of spirotrienones with an ethano linkage between the carbon-carbon triple bond and the methoxy-substituted arene requires a protic solvent and a strong base to achieve high yields. The iodocyclization of propargylic anilides, followed by palladium-catalyzed substitution reactions, affords a rapid increase in molecular complexity and a powerful tool for the preparation of a wide range of functionalized spirotrienones.

Experimental Section

General. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer. High-resolution mass spectra were recorded on a Kratos MS50TC double-focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

The preparation of compounds **1**, **3-6**, **8-9**, **11-12**, **14-21**, **23-24**, **37**, **41-43**, **53-58** and **60** can be found in the supporting information of our previous communication.[19]

Synthesis of Starting Materials.

Compounds **26**, **30** and **32** were prepared by the following general procedure. To a solution of the *N*-arylacetamide (3 mmol) in anhydrous THF (10 mL) was added NaH (9 mmol, 60 % dispersion in mineral oil) at room temperature. After being stirred for 15 min, 3-bromo-1-phenylpropyne (4.5 mmol) in 5 mL of THF was added dropwise to the solution.

TLC was used to monitor completion of the reaction. The reaction was cooled to 0 °C upon completion and quenched with satd aq NH_4Cl, and extracted twice with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford the product.

***N*-(2,4-Dimethoxyphenyl)-*N*-(3-phenylprop-2-ynyl)acetamide (26).** The indicated compound was prepared as a light red sticky oil from *N*-(2,4-dimethoxyphenyl)acetamide in a 42% yield. The reaction mixture was chromatographed using 1:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.11-4.16 (d, J = 17.4 Hz, 2H), 5.12-5.18 (d, J = 17.4 Hz, 2H), 6.48-6.54 (m, 2H), 7.22-7.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.06, 37.83, 55.76, 55.80, 83.86, 85.41, 99.60, 104.55, 123.32, 123.73, 128.28, 128.39, 131.05, 131.82, 156.44, 161.05, 171.49; IR (CH_2Cl_2) 3296, 2967, 1667, 1542, 1466 cm^{-1}; HRMS *m/z* 309.1370 (calcd for $C_{19}H_{19}NO_3$, 309.1365).

***N*-(3-Chloro-4-methoxyphenyl)-*N*-(3-phenylprop-2-ynyl)acetamide (30).** The indicated compound was prepared as a light yellow sticky oil from *N*-(3-chloro-4-methoxyphenyl)acetamide in a 70% yield. The reaction mixture was chromatographed using 1:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.89 (s, 3H), 3.93 (s, 3H), 4.67 (s, 2H), 6.96-6.99 (d, J = 8.7 Hz, 2H), 7.19-7.40 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.71, 39.14, 56.58, 84.60, 84.64, 112.49, 122.89, 123.17, 128.08, 128.48, 128.57, 130.50, 131.88, 135.37, 155.27, 170.35; IR (CH_2Cl_2) 3290, 2965, 1680, 1531 cm^{-1}; HRMS *m/z* 313.0875 (calcd for $C_{18}H_{16}ClNO_2$, 313.0870).

***N*-(4-Methoxy-1-naphthyl)-*N*-(3-phenylprop-2-ynyl)acetamide (32).** To a solution of 4-methoxy-1-naphthamine (340 mg, 2 mmol) in a mixture of 2 mL of NEt_3 and 20 mL of CH_2Cl_2 at 0 °C was slowly added acetyl chloride (236 mg, 3 mmol). The resulting solution

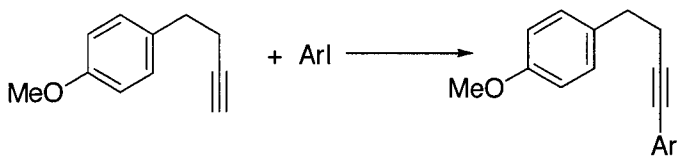
was stirred at 0 °C for 2 h. Then water was added to the mixture and the solution was extracted twice with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography using EtOAc on silica gel to afford *N*-(4-methoxy-1-naphthyl)acetamide (365 mg, 85%). *N*-(4-Methoxy-1-naphthyl)acetamide was treated with NaH and 3-bromo-1-phenylpropyne according to the general procedure to produce compound **32** in an 80% yield as a sticky orange oil. The reaction mixture was chromatographed using EtOAc. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (s, 3H), 3.98 (s, 3H), 4.48-4.53 (d, *J* = 17.4 Hz, 1H), 5.08-5.14 (d, *J* = 17.4 Hz, 1H), 6.78-6.80 (d, *J* = 8.1 Hz, 1H), 7.22-7.23 (m, 5H), 7.43-7.56 (m, 3H), 7.83-7.86 (d, *J* = 7.8 Hz, 1H), 8.32-8.35 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.56, 39.11, 55.92, 84.46, 85.30, 103.53, 122.49, 123.12, 126.18, 127.11, 128.08, 128.40, 131.15, 131.56, 131.78, 156.02, 171.59 (two sp^2 carbons was missing due to overlap); IR (CH_2Cl_2) 3062, 2963, 2846, 1663, 1587, 1398 cm^{-1}; HRMS *m/z* 329.1420 (calcd for $C_{22}H_{19}NO_2$, 329.1416).

***N*-(4-Methoxyphenyl)-*N*-(4-phenylbut-3-ynyl)trifluoromethanesulfonamide (35).** Compound **35** was prepared as follows. To a solution of *N*-(4-methoxyphenyl)trifluoromethanesulfonamide[24] (1.28 g, 5.0 mmol), PPh_3 (5.5 mmol) and 4-phenyl-3-butyn-1-ol (5.5 mmol) in anhydrous THF (50 mL) at 0 °C was added DEAD (5.5 mmol). The resulting solution was stirred at 0 °C for 1 h and an additional 3 h at room temperature. The mixture was washed with brine (50 mL) and the organic layer was dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by chromatography on a silica gel column using 10:1 hexane/EtOAc to afford the product as a colorless oil in a 70% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57-2.61 (t, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.95 (m, 1H), 6.90-6.88 (m, 2H), 7.26-7.31 (m, 5H), 7.38-7.40 (m,

2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.72, 52.12, 55.49, 83.34, 85.02, 114.90, 123.19, 128.18, 128.36, 128.70, 130.58, 131.69; IR ($CHCl_3$) 3048, 3006, 2960, 2840, 1608 cm^{-1}; HRMS *m/z* 383.0810 (calcd for $C_{18}H_{16}F_3NO_3S$, 383.0803).

1-(4-Methoxyphenyl)-4-phenylbut-3-yn-2-ol (38). To a cooled suspension (ice bath) of PCC (4.31 g, 20 mmol) in CH_2Cl_2 (200 mL) was slowly added a solution of 2-(4-methoxyphenyl)ethanol (15 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at that temperature for 2 h, then warmed up to rt for another 2 h. The mixture was filtered through celite and the solvent was removed *in vacuo*. The reaction mixture was chromatographed using 5:1 hexane/EtOAc to give the (4-methoxyphenyl)acetaldehyde as a colorless oil in a 75% yield. To a solution of phenylacetylene (10 mmol) in 30 mL of anhydrous THF at 0 °C was added *n*-BuLi (10 mmol, 2.5 M in hexane) under N_2. The resulting solution was stirred at that temperature for 1 h. Then (4-methoxyphenyl)acetaldehyde (5 mmol) in 10 mL of THF was added to the solution under an inert atmosphere. The resulting solution was stirred at rt for 2 h. Brine (30 mL) was then added to quench the reaction and the solution was extracted twice using diethyl ether (2 x 30 mL). The solvent was removed *in vacuo*, and the reaction mixture was chromatographed using 5:1 hexane/EtOAc to obtain **38** as a light orange oil in an 80% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91 (s, 1H), 2.99-3.01 (d, J = 6.3 Hz, 2H), 3.71 (s, 3H), 4.71 (m, 1H), 6.80-6.83 (d, J = 8.7 Hz, 2H), 7.16-7.26 (m, 5H), 7.35-7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.57, 55.50, 64.07, 85.95, 90.18, 114.09, 122.96, 128.61, 128.70, 129.08, 131.21, 131.95, 158.79; IR (CH_2Cl_2) 3310, 1609 cm^{-1}; HRMS *m/z* 252.1154 (calcd for $C_{17}H_{16}O_2$, 252.1150).

Compounds **44** and **46** were prepared by the Sonogashiro reaction of 1-(3-butynyl)-4-anisole and the corresponding aryl halide. A typical reaction is



described below. To a solution of Et_3N (30 mL), $PdCl_2(PPh_3)_2$ (2 mol %), 3.0 mmol of 4-(3-butynyl)anisole, and 1.2 equiv of aryl iodide (stirring for 3 min beforehand) was added CuI (1 mol %). The reaction mixture was flushed with Ar and the flask was then sealed. The mixture was stirred at room temperature and monitored by TLC to establish completion of the reaction. The resulting solution was filtered, washed with a satd aq NaCl solution, and extracted with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel.

4-(3-Butynyl)anisole. *n*-Butyllithium (3.3 mmol, 1.1 equiv, 2 M in hexanes) was added at -78 °C to 1-(trimethylsilyl)propyne (3.6 mmol, 1.2 equiv.) in dry THF (30 mL). After stirring at -78 °C for 2 h, 4-methoxybenzyl iodide (248 mg, 3 mmol) in dry THF (10 ml) was added and the mixture was stirred at -78 °C for 1 h. The reaction mixture was allowed to reach rt and brine (30 mL) was then added to quench the reaction. The solution was extracted twice using diethyl ether (2 x 30 mL). The solvent was removed under vacuum to afford crude 4-(4-trimethylsilyl-3-butynyl)anisole, which was directly employed in the next step. To the silane was added 20 mL of methanol and KOH (3.6 mmol, 1.2 equiv). The solution was stirred overnight, neutralized by adding 1N HCl, and extracted with ether. The solvent was removed and the product was purified by flash chromatography on silica gel using 40:1 hexane/EtOAc to afford 4-(3-butynyl)anisole in an 80% yield as an oil. The spectral properties were identical with those previously reported.[25]

1,4-Di(4-methoxyphenyl)-1-butyne (44). The indicated compound was prepared in a 70% yield as a sticky oil from the coupling of 4-(3-butynyl)anisole and 4-iodoanisole. The reaction mixture was chromatographed using 40:1 hexane/EtOAc. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59-2.63 (t, *J* = 7.6 Hz, 2H), 2.81-2.84 (t, *J* = 7.6 Hz, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 6.76-6.79 (d, *J* = 8.8 Hz, 2H), 6.81-6.83 (d, *J* = 8.8 Hz, 2H), 7.14-7.16 (d, *J* = 8.8 Hz, 2H), 7.29-7.31 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.11, 34.57, 55.28, 81.17, 88.16, 113.88, 113.95, 116.18, 129.60, 132.97, 133.06, 158.25, 159.22 (one sp^3 C missing due to overlap); IR ($CHCl_3$) 2958, 2916, 2839, 1609, 1511 cm^{-1}; HRMS *m/z* 266.1310 (calcd for $C_{18}H_{18}O_2$, 266.1307).

Ethyl 4-[4-(4-methoxyphenyl)but-1-ynyl]benzoate (46). The indicated compound was prepared in a 65% yield from the coupling of 4-(3-butynyl)anisole and ethyl 4-iodobenzoate. The reaction mixture was chromatographed using 20:1 hexane/EtOAc and the product was obtained as a light yellow solid: mp 50-53 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32-1.37 (t, *J* = 6.9 Hz, 3H), 2.62-2.67 (t, *J* = 7.2 Hz, 2H), 2.81-2.86 (t, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 4.32-4.34 (q, *J* = 6.9 Hz, 2H), 6.81-6.84 (d, *J* = 8.4 Hz, 2H), 7.13-7.16 (d, *J* = 8.1 Hz, 2H), 7.39-7.41 (d, *J* = 8.4 Hz, 2H), 7.93-7.96 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.57, 22.31, 34.36, 55.40, 61.27, 81.18, 93.34, 114.06, 128.86, 129.57, 129.64, 129.72, 131.67, 132.81, 158.48, 166.29; IR ($CHCl_3$) 2990, 2941, 1711, 1607 cm^{-1}; HRMS *m/z* 308.1420 (calcd for $C_{20}H_{20}O_3$, 308.1412).

***p*-Methoxyphenyl 3-phenyl-2-propynyl ether (48).** To a round bottom flask was added 4-methoxyphenol (1.46 g, 11.79 mmol), 3-phenyl-2-propyn-1-ol (1.56 g, 11.79 mmol), triphenylphosphine (2.94 g, 11.20 mmol, 0.95 equiv) and 50 ml of THF. The solution was cooled to 0 °C and diethyl azodicarboxylate (16.51 mmol, 1.4 equiv.) was added dropwise

via syringe. The ice bath was removed and the reaction mixture was stirred under N_2 for 2 h. The solvent was removed and the reaction mixture was chromatographed using 20:1 hexane/EtOAc to obtain **48** (1.82 g, 65%) as a white solid. The spectral properties were identical with those previously reported.[26]

***N*-(3-Phenylprop-2-ynyl)-4-methoxyaniline (50).** To a solution of the methanesulfonate of 3-phenyl-2-propyn-1-ol (1.05 g, 5.0 mmol) in 50 mL of CH_3CN was added 4-methoxyaniline (2.46 g, 20 mmol). After being stirred for 20 h under N_2, the reaction was quenched by adding brine. The reaction mixture was extracted with Et_2O (2 x 30 mL). The extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford the product in a 55% yield as a sticky yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.70-3.80 (br s, 1H), 3.79 (s, 3H), 4.13 (s, 2H), 6.74-6.77 (d, J = 8.7 Hz, 2H), 6.87-6.90 (d, J = 8.7 Hz, 2H), 7.32-7.34 (m, 3H), 7.45-7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.76, 55.98, 83.56, 87.22, 115.10, 115.47, 123.28, 128.49, 128.58, 132.00, 141.58, 153.16; IR ($CHCl_3$) 3331 cm^{-1}; HRMS m/z 237.1158 (calcd for $C_{16}H_{15}NO$, 237.1154).

General Procedure for Iodocyclization by ICl (Conditions A). 0.3 Mmol of the alkyne and 3 mL of CH_2Cl_2 were placed in a vial. Then the vial was sealed, flushed with N_2, and cooled to -78 °C. 2 Equiv of ICl in 1 mL of CH_2Cl_2 were added dropwise to the vial over 10 min. The reaction mixture was stirred at -78 °C for another 10-30 min and then quickly quenched with 20 mL of satd aq $Na_2S_2O_3$ and extracted twice with EtOAc. The organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

1-Acetyl-3-iodo-6-methoxy-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (27). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford a 72% yield of the product as a light orange solid. The product was obtained as a 1:1.6 diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 and 2.13 (s, 3H), 3.73 and 3.78 (s, 3H), 5.47-5.51 (m, 1H), 6.11-6.22 (m, 1H), 6.48-6.65 (m, 1H), 6.90-6.93 (m, 2H), 7.26-7.34 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.54, 22.75, 56.30, 56.60, 63.24, 63.37, 72.55, 72.85, 76.89, 77.32, 77.74, 91.13, 93.62, 104.33, 104.84, 128.47, 128.60, 129.06, 129.21, 129.36, 129.48, 129.53, 129.98, 132.41, 132.53, 142.44, 142.87, 143.98, 145.62, 167.92, 169.00, 170.985, 171.04, 185.89, 186.88; IR (CH_2Cl_2) 3056, 2930, 2859, 1661, 1598, 1398 cm^{-1}; HRMS *m/z* 421.0181 (calcd for $C_{18}H_{16}INO_3$, 421.0175).

1-Acetyl-7-chloro-3-iodo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (31). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford a 60% yield of the product as a light orange solid. The product was obtained as a 1:2.2 diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01 and 2.14 (s, 3H), 4.68 (s, 2H), 6.22-6.32 (d, 1H), 6.73-6.90 (m, 1H), 6.95-7.08 (m, 3H), 7.27-7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.92, 22.89, 62.77, 62.82, 73.07, 73.30, 91.49, 94.11, 128.62, 128.72, 128.79, 129.36, 129.50, 129.57, 129.69, 129.79, 131.98, 132.03, 133.76, 134.44, 142.80, 143.16, 143.26, 144.73, 147.51, 147.57, 168.23, 168.89, 177.00, 177.98; IR (CH_2Cl_2) 2963, 2930, 2867, 1743 cm^{-1}; HRMS *m/z* 424.9686 (calcd for $C_{17}H_{13}ClINO_2$, 424.9680).

2'-Acetyl-1,4-dihydro-5'-iodo-4'-phenylnaphthalene-1-spiro-2'-pyrrol-4-one (33). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford an 80% yield of the product as a light orange solid. The product was obtained as 1:1.7 diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.64 and 2.14 (s, 3H), 4.80-4.93 (m, 2H), 6.32-6.48

(m, 3H), 6.80-6.94 (d, J = 10.0 Hz, 1H), 7.08-7.11 (m, 2H), 7.18-7.22 (m, 1H), 7.39-7.51 (m, 2H), 7.58-7.72 (m, 1H), 7.99-7.80 (d, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.26, 22.92, 63.24, 63.58, 72.42, 72.77, 88.31, 90.78, 125.12, 126.53, 126.74, 126.88, 128.07, 128.14, 128.40, 128.91, 128.94, 129.01, 129.11, 129.23, 129.42, 130.00, 131.29, 131.72, 132.34, 132.40, 133.01, 133.90, 142.89, 142.93, 146.70, 146.92, 147.50, 149.01, 167.29, 169.22, 182.76, 183.64; IR (CH_2Cl_2) 3061, 2860, 1667, 1602, 1398 cm^{-1}; HRMS *m/z* 441.0231 (calcd for $C_{21}H_{16}INO_2$, 441.0226).

4-Iodo-5-phenyl-1-[(trifluoromethyl)sulfonyl]-1-azaspiro[5.5]undeca-4,7,10-trien-9-one (36). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford a 32% yield of the product as a white solid: mp 178-180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.10-3.13 (t, J = 8.0 Hz, 2H), 3.86-3.88 (t, J = 8.0 Hz, 2H), 6.10-6.13 (d, J = 10.4 Hz, 2H), 6.85-6.90 (m, 4H), 7.23-7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.84, 44.93, 64.78, 102.59, 127.63, 128.76, 130.19, 130.69, 139.24, 143.27, 183.60; IR ($CHCl_3$) 3062, 2921, 1670, 1398 cm^{-1}; HRMS *m/z* 494.9627 (calcd for $C_{17}H_{13}F_3INO_3S$, 494.9613). Crystals for x-ray crystallography were obtained by slow evaporation of the compound in 5:1 hexane/EtOAc.

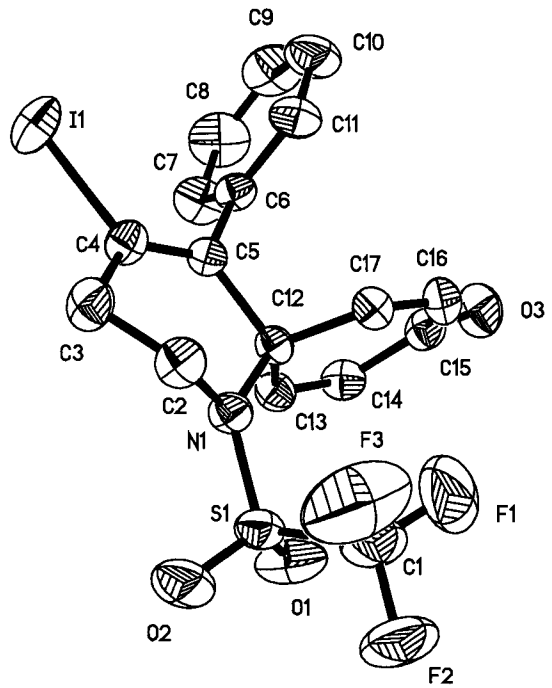


Figure 1. ORTEP drawing of **36**.

General Procedure for Iodo/bromocyclization by Br_2/I_2 (Conditions B). 0.3 Mmol of the alkyne, 0.60 mmol of $NaHCO_3$ and 3 mL of MeCN were placed in a vial. 2 Equiv of Br_2/I_2 in 1 mL of MeCN were added dropwise to the vial. The reaction mixture was stirred for 10 min (Br_2) or 1-12 h (I_2). The reaction mixture was then quenched with 20 mL of satd aq $Na_2S_2O_3$ and extracted twice with EtOAc. The organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

3-Bromo-4-(4-methoxyphenyl)-1-trifluoromethanesulfonyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (7). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford a 95% yield of the product as a yellow solid: mp 143-146 °C; ^1H NMR ($CDCl_3$, 400

MHz) δ 3.78 (s, 3H), 4.71 (s, 2H), 6.22-6.24 (d, J = 10.4 Hz, 2H), 6.82-6.86 (m, 4H); 7.01-7.03 (d, J = 10.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.26, 59.34, 74.13, 114.01, 115.40, 121.55, 130.50, 137.98, 160.41, 144.40, 183.70 (one carbon was missing due to overlap); IR (CH_2Cl_2) 2959, 2934, 1671, 1631, 1397 cm^{-1}; HRMS *m/z* 462.9712 (calcd for $C_{17}H_{13}BrF_3NO_4S$, 462.9701).

4-(4-Acetylphenyl)-3-bromo-1-trifluoromethanesulfonyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (10). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford a 30% yield of the product as a yellow solid: mp 162-165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.60 (s, 3H), 4.75 (s, 2H), 6.23-6.26 (d, J = 9.9 Hz, 2H), 6.87-6.90 (d, J = 10.2 Hz, 2H), 7.19-7.22 (d, J = 8.7 Hz, 2H), 7.90-7.93 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.86, 59.74, 74.31, 116.84, 128.64, 129.80, 130.93, 134.41, 137.63, 137.97, 144.01, 183.46, 197.32; IR (CH_2Cl_2) 2962, 2925, 1686, 1673, 1397 cm^{-1}; HRMS *m/z* 474.9712 (calcd for $C_{18}H_{13}BrF_3NO_4S$, 474.9701).

3-Bromo-4-butyl-1-trifluoromethanesulfonyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (13). The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford a 31% yield of the product as a yellow solid: mp 98-99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85-0.88 (t, J = 7.2 Hz, 3H), 1.25-1.39 (m, 4H), 1.83-1.87 (m, 2H), 4.56 (s, 2H), 6.35-6.37 (d, J = 10.4 Hz, 2H), 6.69-6.72 (d, J = 10.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.61, 22.78, 25.87, 30.67, 59.17, 74.19, 113.50, 121.30, 130.29, 137.34, 144.75, 183.95 (extra peak due to F-splitting); IR (CH_2Cl_2) 2959, 2934, 1671, 1631, 1397 cm^{-1}; HRMS *m/z* 412.9917 (calcd for $C_{14}H_{15}BrF_3NO_3S$, 412.9908).

3-Bromo-4-(cyclohex-1-en-1-yl)-2-methyl-1-trifluoromethanesulfonyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (22). The reaction mixture was chromatographed using

10:1 hexane/EtOAc to afford a 67% yield of the product as a yellow solid: mp 132-135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51-1.68 (m, 7H), 1.91-2.02 (m, 4H), 4.70-5.00 (m, 1H), 5.50 (m, 1H), 6.27-6.29 (d, J = 9.6 Hz, 2H), 6.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.25, 22.31, 28.35, 67.08, 74.26, 120.53, 127.73, 133.13, 138.52, 184.02 (4 carbons missing due to overlap); IR (CH_2Cl_2) 2933, 2859, 1674, 1631, 1396 cm^{-1}; HRMS *m/z* 451.0074 (calcd for $C_{17}H_{17}BrF_3NO_3S$, 451.0065).

1-Acetyl-3-bromo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (25). The reaction mixture was chromatographed using EtOAc to afford a 60% yield of the product as a yellow solid (conformational isomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01 and 2.15 (s, 3H), 4.68 and 4.69 (s, 2H), 6.20-6.29 (m, 2H), 6.74-6.77 (d, J = 10.0 Hz, 1H), 6.86-6.89 (d, J = 10.0 Hz, 1H), 7.05-7.07 (m, 2H), 7.27-7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.88, 22.97, 58.60, 58.94, 71.49, 71.91, 116.19, 118.90, 128.44, 128.54, 129.39, 129.48, 129.50, 129.74, 130.33, 130.45, 130.58, 130.86, 137.41, 139.23, 146.87, 147.06, 168.35, 169.37, 183.76, 184.76; IR (CH_2Cl_2) 3054, 2917, 1669, 1626, 1396 cm^{-1}; HRMS *m/z* 343.9968 (calcd for $C_{17}H_{14}BrNO_2$, 343.9960).

1-Acetyl-3-bromo-6-methoxy-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (28). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford a 54% yield of the product as a yellow solid. The product was obtained as a 1:1.5 diastereomeric mixtures. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92 and 2.13 (s, 3H), 3.74 and 3.79 (s, 3H), 4.64-4.65 (m, 2H), 5.50-5.54 (m, 1H), 6.14-6.24 (m, 1H), 6.50-6.67 (m, 1H), 6.95-6.99 (m, 2H), 7.28-7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.34, 22.54, 56.13, 56.42, 58.98, 59.28, 72.42, 72.74, 104.23, 104.72, 116.44, 118.98, 128.32, 128.44, 128.86, 129.01, 129.22, 129.33, 129.52, 129.97, 130.23, 130.37, 137.70, 139.20, 142.22, 142.70, 167.89, 169.02,

170.66, 170.82, 185.69, 186.69; IR (CH_2Cl_2) 3054, 2939, 1659, 1598 cm^{-1}; HRMS *m/z* 373.0320 (calcd for $C_{18}H_{16}BrNO_3$, 373.0314).

1-Acetyl-3,9-dibromo-6-methoxy-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (29). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford a 45% yield of the product as light a yellow solid. The product was obtained as a 1:2.8 diastereomeric mixtures. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93 and 2.14 (s, 3H), 3.73 and 3.79 (s, 3H), 4.63-4.64 (m, 2H), 5.57-5.61 (m, 1H), 6.95-6.98 (m, 2H), 7.00 and 7.16 (s, 1H), 7.31-7.34 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.37, 22.41, 56.54, 56.88, 58.99, 59.17, 74.50, 74.63, 102.73, 103.14, 117.02, 119.52, 125.31, 125.85, 128.51, 128.63, 128.81, 128.98, 129.44, 129.59, 129.79, 129.89, 137.19, 138.59, 142.20, 142.46, 167.88, 168.78, 170.93, 171.12, 178.17, 179.11; IR (CH_2Cl_2) 3054, 2940, 1658, 1597 cm^{-1}; HRMS *m/z* 450.9425 (calcd for $C_{18}H_{15}Br_2NO_3$, 450.9419).

2'-Acetyl-5'-bromo-4'-phenyl-1,4-dihydronaphthalene-1-spiro-2'-pyrrol-4-one (34). The reaction mixture was chromatographed using 1:1 hexane/EtOAc to afford an 82% yield of the product as a light brown solid. The product was obtained as a 1:1.7 diastereomeric mixture. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.64 and 2.14 (s, 3H), 4.84-4.93 (m, 2H), 6.32-6.54 (m, 3H), 6.81-6.95 (d, J = 10.0 Hz, 1H), 7.08-7.12 (m, 2H), 7.18-7.22 (m, 1H), 7.39-7.54 (m, 2H), 7.58-7.73 (m, 1H), 7.99-8.01 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.21, 22.89, 59.14, 59.63, 72.39, 72.72, 114.06, 116.48, 125.20, 126.60, 126.74, 126.90, 128.10, 128.17, 128.45, 128.87, 128.97, 129.04, 129.08, 129.31, 129.56, 130.13, 130.43, 131.34, 131.78, 133.07, 133.97, 141.23, 142.51, 142.83, 142.92, 146.66, 146.84, 167.47, 169.41, 182.74, 183.65; IR (CH_2Cl_2) 3056, 3861, 1658, 1600, 1401 cm^{-1}; HRMS *m/z* 393.0372 (calcd for $C_{21}H_{16}BrNO_2$, 393.0364).

2-Bromo-3-hydroxy-1-phenylspiro[4.5]deca-1,6,9-trien-8-one (40). The reaction mixture was chromatographed using EtOAc to afford a 50% yield of the product as a white solid (Conditions B): mp 142-143 °C (decomposes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05-2.30 (m, 1H), 2.59-2.65 (m, 1H), 2.79 (s, 1H), 5.02-5.04 (m, 1H), 6.24-6.29 (m, 2H), 6.79-6.82 (m, 1H), 6.99-7.02 (m, 1H), 7.19-7.23 (m, 2H), 7.26-7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.65, 55.76, 78.24, 127.00, 127.77, 128.33, 128.89, 129.17, 129.72, 133.17, 144.11, 151.78, 152.72, 185.42; IR (CH_2Cl_2) 3368, 1615 cm^{-1}; HRMS *m/z* 316.0105 (calcd for $C_{16}H_{13}BrO_2$,316.0099).

General Procedure for Iodo/bromocyclization by Br_2/ICl (Conditions C). 0.3 Mmol of the alkyne, 0.6 mmol of NaOMe, 4 mL of MeOH, and 2 mL of CH_2Cl_2 were placed in a vial and the solution was cooled to -78 °C. 5 Equiv of Br_2/ICl in 1 mL of CH_2Cl_2 were added dropwise to the vial. The reaction mixture was stirred for 10 min, quickly quenched with 20 mL of satd aq $Na_2S_2O_3$, and extracted twice with EtOAc. The organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

3-Hydroxy-2-iodo-1-phenylspiro[4,5]deca-1,6,9-trien-8-one (39). The reaction mixture was chromatographed using EtOAc to afford an 87% yield of the product as a yellow solid: mp 168-170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32-2.36 (m, 1 H), 2.61-2.67 (m, 2H), 5.02-5.04 (m, 1H), 6.21-6.26 (m, 2H), 6.76-6.79 (m, 1H), 6.95-6.98 (m, 1H), 7.12-7.13 (m, 2H), 7.26-7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.02, 56.87, 81.10, 106.18, 127.74, 128.32, 128.83, 129.15, 129.65, 134.94, 150.50, 151.31, 152.34, 185.39; IR (CH_2Cl_2) 3369, 1667, 1613 cm^{-1}; HRMS *m/z* 363.9968 (calcd for $C_{16}H_{13}IO_2$, 363.9960).

2-Bromo-1-phenylspiro[4.5]deca-1,6,9-trien-8-one (43). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford a 98% yield of the product as a light yellow solid: mp 129-130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28-2.33 (t, J = 7.2 Hz, 1H), 3.00-3.05 (t, J = 7.2 Hz, 1H), 6.22-6.25 (d, J = 10.2 Hz, 2H), 6.90-6.94 (d, J = 10.2 Hz, 2H), 7.16-7.19 (m, 2H), 7.25-7.28 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.17, 39.45, 56.88, 123.52, 128.14, 128.39, 128.54, 129.36, 134.12, 141.37, 152.23, 185.72; IR (CH_2Cl_2) 3038, 2944, 2858, 1665, 1620 cm^{-1}; HRMS *m/z* 300.0155 (calcd for $C_{16}H_{13}BrO$, 300.0150).

2-Iodo-1-(4-methoxyphenyl)spiro[4.5]deca-1,6,9-trien-8-one (45). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford a 92% yield of the product as a white solid: mp 134-135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29-2.33 (t, J = 7.2 Hz, 1H), 3.02-3.05 (t, J = 7.2 Hz, 1H), 3.76 (s, 3H), 6.20-6.22 (d, J = 10.0 Hz, 2H), 6.77-6.80 (d, J = 8.4 Hz, 2H), 6.87-6.90 (d, J = 10.0 Hz, 2H), 7.05-7.07 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.54, 43.36, 55.20, 56.72, 98.34, 113.58, 127.87, 129.07, 129.30, 147.30, 152.00, 159.43, 185.60; IR (CH_2Cl_2) 3055, 2958, 2833, 1665, 1598, 1505 cm^{-1}; HRMS *m/z* 378.0123 (calcd for $C_{17}H_{15}IO_2$, 378.0117).

Ethyl 4-(2-bromo-8-oxospiro[4.5]deca-1,6,9-trien-1-yl)benzoate (47). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford a 36% yield of the product as a light yellow solid: mp 108-109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.39 (t, J = 7.2 Hz, 3H), 2.31-2.35 (t, J = 7.6 Hz, 2H), 3.04-3.07 (t, J = 7.6 Hz, 2H), 4.33-4.38 (q, J = 7.2 Hz, 2H), 6.24-6.26 (d, J = 9.6 Hz, 2H), 6.90-6.92 (d, J = 9.6 Hz, 2H), 7.25-7.27 (d, J = 6.3 Hz, 2H), 7.94-7.96 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.35, 36.03, 39.43, 56.71, 61.08, 124.62, 127.99, 129.39, 129.46, 130.29, 138.50, 140.50, 151.47, 166.09,

185.21; IR (CH_2Cl_2) 2982, 2940, 2857, 1719, 1666 cm^{-1}; HRMS *m/z* 372.0369 (calcd for $C_{19}H_{17}BrO_3$, 372.0361).

3-Iodo-6-methoxy-4-phenylquinoline (52). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product in a 45% yield as a white solid: mp 153-154 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H), 6.69-6.68 (d, J = 2.4 Hz, 1H), 7.26-7.28 (m, 2H), 7.34-7.37 (m, 1H), 7.52-7.58 (m, 3H), 7.99-8.01 (d, J = 9.2 Hz, 1H), 9.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.42, 97.01, 104.80, 122.08, 128.67, 128.79, 129.00, 130.99, 140.67, 143.42, 150.85, 154.17, 158.30; IR ($CHCl_3$) 2837, 1613, 1513, 1483, 1246 cm^{-1}; HRMS *m/z* 360.9972 (calcd for $C_{16}H_{12}INO$, 360.9964).

General Procedure for Iodocyclization by ICl (Conditions D). 0.3 Mmol of the alkyne and 2 mL of MeCN were placed in a vial. 1.5 Equiv of ICl in 1 mL of MeCN were added dropwise to the vial. The reaction mixture was stirred for 10 min, quenched with 20 mL of satd aq $Na_2S_2O_3$, and extracted twice with EtOAc. The organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

4-(4-Acetylphenyl)-3-phenyl-1-trifluoromethanesulfonyl-1-azaspiro[4.5]deca-3,6,9-trien-8-one (59) To a solution of **9** (0.25 mmol) in 4 mL of DME in a vial was added phenylboronic acid (0.375 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and CsF (0.75 mmol). The vial was flushed with N_2 gas and closed. The reaction mixture was heated to 40 °C for 48 h, cooled to room temperature, diluted with 25 ml of ether, washed with 25 mL of satd aq NaCl, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford a 41 % yield of the product as a yellow solid: mp 172-173 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.58 (s, 3H),

5.03 (s, 2H), 6.21-6.24 (d, J = 10.4 Hz, 2H), 6.94-7.01 (m, 4H), 7.14-7.26 (m, 5H), 7.84-7.86 (d, J = 10.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 26.63, 57.65, 127.76, 128.45, 128.60, 128.82, 129.57, 129.71, 130.28, 131.01, 132.85, 136.42, 137.26, 183.74, 197.34; IR (CH_2Cl_2) 3056, 2926, 2856, 1676, 1394 cm^{-1}; HRMS *m/z* 473.0914 (calcd for $C_{24}H_{18}F_3NO_4S$, 473.0909).

Acknowledgement. We gratefully acknowledge the National Institute of General Medical Science (GM 070620) for support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. for donations of palladium acetate. The phenylboronic acid was contributed by Frontier Scientific, Inc.

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Chapter 5. Palladium-Catalyzed Annulation of Arynes by 2-Halobenzaldehydes: Synthesis of Fluoren-9-ones

Based on a communication published in *Organic Letters*

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Abstract

Arynes, generated *in situ* from 2-(trimethylsilyl)aryl triflates and CsF, undergo annulation by *o*-haloarenecarboxaldehydes in the presence of a Pd catalyst, providing a useful new method for the synthesis of fluoren-9-ones in good yields.

Introduction

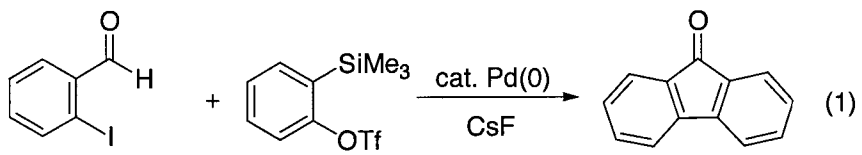
The transition metal-catalyzed transformations of arynes have recently received considerable attention. Pioneering work in this area involved the cyclotrimerization of arynes[1] and the cocyclization of arynes with alkynes.[2] More recently, metal-catalyzed carbonylative cycloadditions of arynes[3] and the cocyclotrimerization of arynes with bicyclic alkenes[4] and allenes[5] have been reported. Great progress has also been made in the addition of element-element σ-bonds to arynes, including Si-Si,[6] C-Sn,[7] and Sn-Sn[8] bonds. There are also a few examples of the addition of π-allylpalladium compounds to arynes.[9]

The palladium-catalyzed annulation of alkynes by functionally-substituted aryl halides has proven to be a very efficient method for the construction of a wide variety of heterocycles and carbocycles.[10] However, similar carbopalladation reactions of arynes are

unprecedented to the best of our knowledge.[11] Our continuing interest in such chemistry prompted us to explore such possibilities. Herein, we report the first example of the palladium-catalyzed annulation of arynes by *o*-halobenzaldehydes.[12] This provides a convenient synthesis of fluoren-9-ones, which are of considerable interest because of their important biomedical applications[13] and their use as key synthetic intermediates.[14]

Results and Discussions

The high reactivity[15] and short lifetime of benzyne and other arynes suggest that their use as a component of a catalytic reaction might be difficult. Therefore, our preliminary efforts focused on the optimization of reaction conditions for the reaction of 2-iodobenzaldehyde (**1**) with silylaryl triflate **2**, which we have observed to afford fluoren-9-one (**3**) (eq 1). 0.30 Mmol of **1** was initially treated with 3 equiv of silylaryl



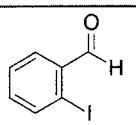
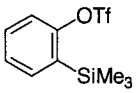
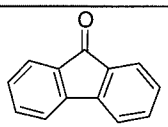
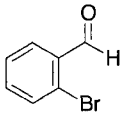
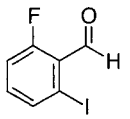
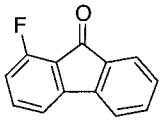
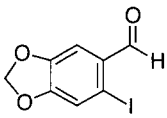
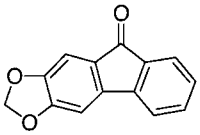
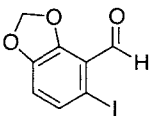
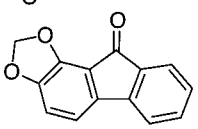
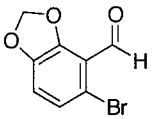
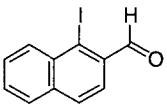
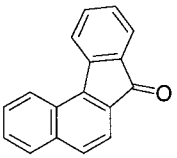
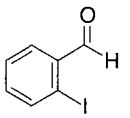
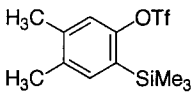
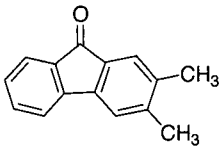
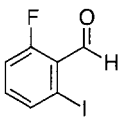
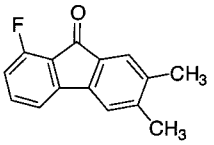
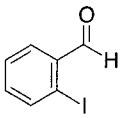
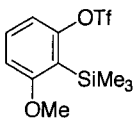
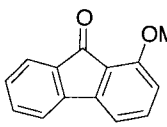
1 **2** **3**

triflate **2** plus 3 equiv of CsF, a combination known to generate benzyne,[16] along with 5 mol % $Pd(OAc)_2$ and 5 mol % P(*o*-tolyl)$_3$ as the catalyst in 4 mL of MeCN at 70 °C. The desired product **3** was obtained in a 36% yield. The yield was improved to 51% when using 2 mL of toluene and 2 mL of MeCN as the solvent. Other solvents, such as THF, DMF, and toluene alone, all gave poor yields (0-24%). The choice of base was also crucial for the success of the reaction. Replacement of CsF with KF, or utilizing NEt_3 or Cs_2CO_3 as a base together with CsF greatly decreased the yield. Using pyridine, none of the desired product was generated at all. Control experiments revealed that in the absence of the palladium catalyst or the CsF, no fluorenone **3** was obtained. Variation of the Pd catalyst and ligands had a

minimal effect. For example, 5 mol % $Pd(dba)_2$ with 5 mol % P(*o*-tolyl)$_3$ improved the yield to 59%. Similar yields (50-57%) were obtained using $Pd(dba)_2$ plus dppf or 2-(dicyclohexylphosphino)biphenyl. The ligand dppe provided only a 38% yield of **3**. The yield was dramatically improved to 75% when 5 equiv of silylaryl triflate **2** and 5 equiv CsF were used at 110 °C. Therefore, the following reaction conditions were chosen as our 'optimal' conditions: 0.30 mmol of aryl halide, 5 equiv of the silylaryl triflate, 5 equiv of CsF, 5 mol % $Pd(dba)_2$, 5 mol % P(*o*-tolyl)$_3$ in 4 mL of 1:1 toluene/MeCN at 110 °C for 12 h.

This palladium-catalyzed annulation reaction was successfully extended to other *o*-haloarenecarboxaldehydes and substituted arynes (Table 1). When *o*-bromobenzaldehyde was employed as the aryl halide, a yield comparable to that of *o*-iodobenzaldehyde was obtained, although a much longer reaction time was required (compare entries 1 and 2, Table 1). The addition of a fluorine substituent on the aromatic ring of the aldehyde improved the yield to 82% (entry 3). This could be because the electron-withdrawing fluorine facilitates oxidative addition of the aryl iodide to the palladium and at the same time increases the electrophilicity of the carbonyl group (see the later mechanistic discussion). On the other hand, the reaction of 2-iodo-4,5-methylenedioxybenzaldehyde (**7**) with triflate **2** generated fluorene-9-one derivative **8** in only a 56% yield (entry 4). One might be tempted to attribute this to the electron-rich nature of the aromatic ring. The corresponding 2-bromobenzaldehyde afforded an even lower yield. However, electron-rich 2-iodo-5,6-methylenedioxybenzaldehyde (**9**) reacts smoothly with triflate **2** to provide the desired product **10** in a 72% yield (entry 5). Even annulation with the corresponding aryl bromide **11** proceeded without problem in a moderate yield (entry 6). The reaction was also successfully applied to naphthaldehyde

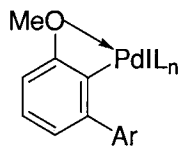
Table 1. Synthesis of Fluoren-9-ones by the Palladium-Catalyzed Annulation of Silylaryl Triflates by *o*-Haloarenecarboxaldehydes[a]

	aryl halide		silylaryl triflate		product		% yield
1		**1**		**2**		**3**	75
2		**4**		**2**		**3**	73[b]
3		**5**		**2**		**6**	82
4		**7**		**2**		**8**	56
5		**9**		**2**		**10**	72
6		**11**		**2**		**10**	50
7		**12**		**2**		**13**	48
8		**1**		**14**		**15**	71
9		**5**		**14**		**16**	73
10		**1**		**17**		**18**	61[c]

[a] All reactions were run under the following conditions unless otherwise specified: 0.30 mmol of *o*-halobenzaldehyde, 5 equiv of silylaryl triflate, 5 equiv of CsF, 5 mol % of $Pd(dba)_2$, and 5 mol % of P(*o*-tolyl)$_3$ in 4 mL of 1:1 MeCN/toluene were heated at 110 °C for 12 h. [b] This reaction needed 24 h to reach completion and the yield was determined by GC-MS. [c] The yield of the other isomer was 7% according to gas chromatographic analysis.

12 (entry 7). The slightly lower yield here might be due to the fact that the iodide is located on the sterically-hindered 1 position of the naphthalene, thereby slowing down the oxidation addition to Pd and/or hindering aryne annulation.

In addition to **2**, other substituted aryne precursors have also been successfully exploited in this process. Thus, triflate **14** with two methyl groups on the phenyl ring furnished products **15** and **16** in 71% and 73% yields, respectively (entries 8 and 9). Reaction with 3-methoxybenzyne (from triflate **17**) showed good regioselectivity affording the two possible isomeric fluoren-9-ones in a 9:1 ratio as determined by GC-MS analysis. Compound **18** is the major product as determined by comparison of its ^{1}H and ^{13}C NMR spectra with those of the known compound.[17] Fluoren-9-one **18** is apparently formed by preferential formation of intermediate **19**, which may be favored due to coordination of the methoxy group to Pd.[3,18] Intermediate **19** is also the product one would expect from the more anionic aryl moiety of ArPdX adding to the more remote carbon of the aryne. In addition, as observed in the carbopalladation of alkynes,[10] Pd may prefer to add to the more hindered end of the aryne, which is *ortho* to the methoxy group.

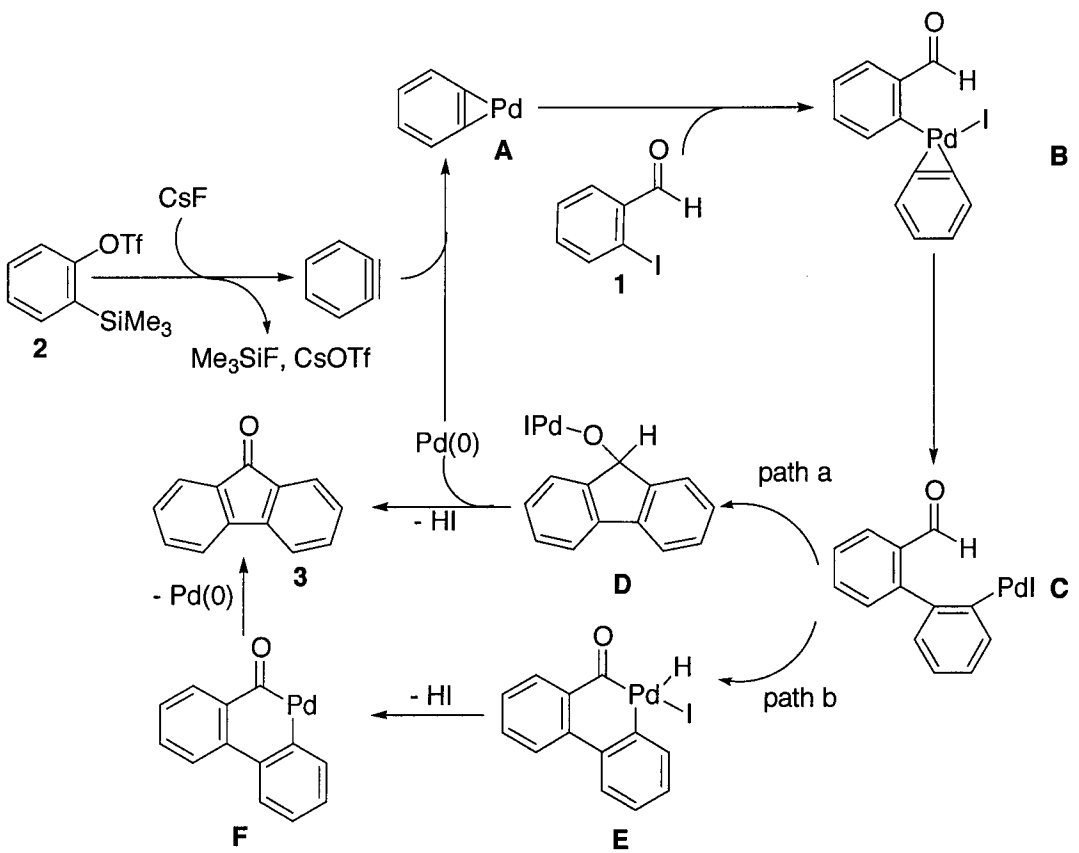


19

Based on the known chemistry of organopalladium compounds and alkynes, the following mechanism is proposed (ligands are omitted for simplicity, Scheme 1). First, the aryne generated from the triflate coordinates with Pd(0), affording palladacycle **A**. Oxidative addition of the aryl iodide to **A** generates arylpalladium(IV) complex **B**. Reductive elimination affords a new arylpalladium intermediate **C**. Intermediate **C** can either add to the

carbonyl group[19] and subsequently undergo β-hydride elimination (path a) or the aldehyde C-H bond may oxidatively add[20] to the palladium to produce an organopalladium(IV) intermediate **E**, which subsequently undergoes rapid reductive elimination to provide the desired product and regenerate the Pd(0) catalyst (path b). The exact pathway is unclear.

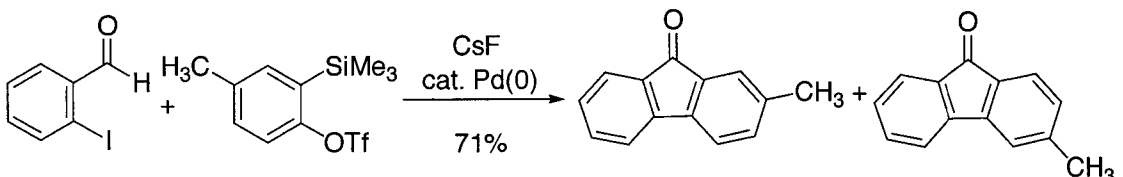
Scheme 1



The involvement of an aryne in this catalytic reaction is strongly supported by the results of the reaction between **1** and **20**, which affords a 71% yield of a mixture of two regioisomeric products **21** and **22** in a nearly 1:1 ratio as determined by GC-MS and ^{1}H NMR spectroscopic analysis (Scheme 2). This observation indicates that the aryl group of the starting aryl halide adds about equally to the two carbons originally attached to the silyl and

OTf groups, in agreement with the formation of an aryne from **20** prior to reaction with the aldehyde **1**.

Scheme 2



1 **20** **21** **22**

Conclusions

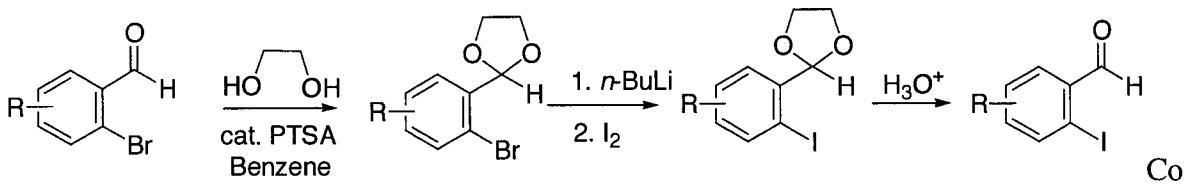
In conclusion, we have developed a new palladium-catalyzed annulation reaction of arynes by 2-haloarenecarboxaldehydes. This method provides an efficient synthesis of substituted fluoren-9-ones from readily available starting materials. Extension of this methodology to the synthesis of other biological interesting heterocycles and carbocycles, and the exploration of similar protocols with other functionally-substituted haloarenes and arynes are underway.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

Synthesis of Starting Materials. Compounds **1, 2, 4** and **11** were purchased from Sigma-Aldrich Co. Compounds **5**,[21] **14**,[22] **17**[2a] and **20**[9b] were prepared according to literature procedures.

Compounds **7, 9** and **12** were prepared from the respective commercially available 2-bromoarenecarboxaldehydes by a previously reported three-step procedure.[23]



Compound **7** was obtained as a light yellow solid in a 75% overall yield. The spectral properties were identical with those previously reported.[5] Compound **9** was obtained as a white solid in an 80% overall yield. The spectral properties were identical with those previously reported.[24]

1-Iodo-2-naphthalenecarboxaldehyde (12). Compound **12** was obtained as a light yellow solid in a 60% overall yield: mp 106-107 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57-7.60 (m, 2H), 7.70-7.73 (m, 2H), 7.78-7.81 (d, J = 8.7 Hz, 1H), 8.31-8.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 124.96, 128.71, 128.83, 129.50, 129.94, 133.45, 134.03, 134.61, 137.10, 197.72; IR ($CHCl_3$) 1680 cm^{-1}; HRMS m/z 281.9545 (calcd for $C_{11}H_7IO$, 281.9542).

General Procedure for the Palladium-Catalyzed Synthesis of Fluoren-9-ones. The 2-iodobenzaldehyde (0.30 mmol), the 2-(trimethylsilyl)aryl triflate (1.50 mmol), CsF (1.50 mmol), $Pd(dba)_2$ (0.015 mmol), P(o-tolyl)$_3$ (0.015 mmol), 2 mL of toluene, and 2 mL of MeCN were placed in a 4 dram vial and the vial was sealed. The reaction mixture was stirred first at room temperature for 1 min and then heated to 110 °C for 12 h. The mixture was allowed to cool to room temperature (CAUTION: OPENING THE VIAL AT A HIGH

TEMPERATURE CAN BE DANGEROUS!), diluted with diethyl ether, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel.

Compounds **3**,[25] **13**,[17a] **18**,[17b] **21**,[17b] and **22**[17b] were obtained after flash chromatography, and their spectral properties are identical with these previously reported.

1-Fluoro-9*H*-fluoren-9-one (6). The indicated compound was obtained as a yellow solid in an 82% yield. The reaction mixture was chromatographed using 10:1 hexane/EtOAc: mp 117-119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89-6.95 (t, J = 8.4 Hz, 1H), 7.29-7.35 (m, 2H), 7.43-7.53 (m, 3H), 7.65-7.67 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 116.61, 116.65, 117.59, 117.87, 120.12, 120.29, 120.88, 124.69, 129.90, 134.19, 134.86, 137.23, 137.34, 143.59, 143.63, 146.56, 146.61, 157.79, 161.29, 190.36 (extra peaks due to F splitting); IR ($CHCl_3$) 2923, 1716, 1600, 1471 cm^{-1}; HRMS *m/z* 198.0485 (calcd for $C_{13}H_7FO$, 198.0481).

9*H*-Fluoreno[2,3-*d*][1,3]dioxol-9-one (8). The reaction mixture was chromatographed using 10:1 hexane/EtOAc and the indicated compound was obtained as a yellow solid in a 56% yield: mp 145-147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.05 (s, 2H), 6.95 (s, 1H), 7.09 (s, 1H), 7.18-7.22 (m, 1H), 7.31-7.33 (d, J = 7.6 Hz, 1H), 7.39-7.43 (m, 1H), 7.53-7.55 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.76, 102.27, 105.18, 119.31, 123.81, 128.39, 128.71, 134.38, 134.76, 141.74, 143.67, 148.50, 153.37, 192.45; IR ($CHCl_3$) 1709, 1593, 1477, 1458 cm^{-1}; HRMS *m/z* 224.0476 (calcd for $C_{14}H_8O_3$, 224.0473).

10*H*-Fluoreno[1,2-*d*][1,3]dioxol-10-one (10). The reaction mixture was chromatographed using 20:1 hexane/EtOAc and the indicated compound was obtained as a yellow solid in a 72% yield (from the aryl iodide) or 50 % (from the aryl bromide): mp 161-

163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (s, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.24-7.26 (m, 1H), 7.45-7.46 (m, 2H), 7.65 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 103.05, 111.96, 113.60, 115.44, 119.94, 124.41, 128.21, 134.24, 134.62, 136.89, 144.60, 145.00, 150.44, 190.92; IR ($CHCl_3$) 1710, 1468, 1250 cm^{-1}; HRMS *m/z* 224.0478 (calcd for $C_{14}H_8O_3$, 224.0473).

2,3-Dimethyl-9*H*-fluoren-9-one (15). The reaction mixture was chromatographed using 20:1 hexane/EtOAc and the indicated compound was obtained as a yellow solid in a 71% yield: mp 88-89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.25 (m, 2H), 7.41-7.43 (m, 3H), 7.59 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.95, 20.77, 119.84, 121.82, 124.11, 125.59, 128.55, 132.34, 134.41, 134.64, 137.62, 142.55, 144.19, 144.65, 194.12; IR ($CHCl_3$) 2922, 1707, 1601, 1452 cm^{-1}; HRMS *m/z* 208.0891 (calcd for $C_{15}H_{12}O$, 208.0888).

1-Fluoro-6,7-dimethyl-9*H*-fluoren-9-one (16). The reaction mixture was chromatographed using 20:1 hexane/EtOAc and the indicated compound was obtained as a yellow solid in a 73% yield: mp 165-167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.29 (s, 3H), 6.82-6.87 (t, J = 8.8 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.21 (s, 1H), 7.36-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.99, 20.73, 115.92, 115.95, 116.88, 117.09, 120.20, 120.32, 122.07, 125.60, 132.10, 136.70, 136.78, 138.39, 141.48, 141.51, 144.24, 146.62, 146.66, 157.91, 160.52, 190.35 (extra peaks are due to F-splitting); IR ($CHCl_3$) 2920, 1713, 1618, 1454 cm^{-1}; HRMS *m/z* 226.0798 (calcd for $C_{15}H_{11}FO$, 226.0794).

Acknowledgements. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institute of General Medical Sciences (GM 070620) for partial support of this research and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. for donating the palladium acetate.

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GENERAL CONCLUSIONS

In this dissertation, the scope and limitations of several palladium-catalyzed and electrophilic cyclization processes have been presented, which result in the synthesis of 1,3-dienes, quinolines, naphthalenes, naphthols, spiro[4.5]trienones and fluoren-9-ones.

Chapter 1 describes the synthesis of 1,3-dienes and 1,3,5-trienes by the Pd-catalyzed coupling reaction of vinylic halides, internal alkynes and organoboranes. The reaction proceeds very well when electron-rich aryl iodides and various arylboronic acids are employed. When vinylic boronic acids are employed, 1,3,5-trienes can be synthesized in moderate yields. Two regioisomers are usually obtained when unsymmetrical internal alkynes are employed.

Chapter 2 reports the concise and efficient synthesis of substituted quinolines by either the electrophilic or $Hg(OTf)_2$-catalyzed cyclization of *N*-(2-alkynyl)anilines and *N*-(2-alkynyl)triflamides. The groups in the 4 position of the quinoline range from aryl to alkyl to vinylic.

Chapter 3 extends the electrophilic cyclization strategy to the synthesis of naphthalenes, 2-naphthols, carbazoles and dibenzothiophenes, which are prepared in excellent yields. Arene-containing propargylic alcohols, methyl ethers, propargylic esters and 1-aryl-3-alkyn-2-ones are all versatile starting materials for this process.

Chapter 4 presents the synthesis of a variety of spiro[4.5]trienones by the cyclization of 4-(*p*-methoxyaryl)alkynes. Different reaction conditions have been developed for different substrates. ICl, I_2 and Br_2 are all effective electrophiles. *Ipso* and *ortho* cyclization can be turned "on" and "off" by the presence or absence of a base.

Chapter 5 describes an unprecedented palladium-catalyzed annulation of a variety of arynes to synthesize fluoren-9-ones. Extensive optimization studies have revealed the best results are obtained by employing an aryl halide, 5 equiv of a silylaryl triflate, 5 equiv of CsF, 5 mol % $Pd(dba)_2$, and 5 mol % P(*o*-tolyl)$_3$ in 1:1 toluene/MeCN at 110 °C. The effect on the yield of fluorenone of varying the substituents on the aryl iodide and the aryl triflate is discussed.

ACKNOWLEDGEMENT

First, I would like to take this opportunity to express my sincere gratitude and appreciation to my major professor, Richard C. Larock, for his incredible patience towards a beginner like me, his excellent guidance, and for financial support throughout the course of this study. I feel very fortunate to have had this great chance to work in his lab for the past five years.

I want to thank all of the professors who have taught me fascinating chemistry and all of my committee members for providing me both academic and personal help.

I would like to thank former and current members of the Larock group. It has been my great pleasure being with all of you guys. In particular, I would like to thank Dr. Daniel E. Emrich, Dr. Marino A. Campo, Dr. Haiming Zhang, Dr. Guangxiu Dai, Dr. Qinhua Huang and Mr. Zhijian Liu for their assistance and valuable discussions during the early stages of this study.

I would like to thank my parents and parents-in-law for their sacrifices, enormous love and moral support.

Finally, I want to thank my husband Tuanli, whose love, encouragement, support and inspiration helped me with every page of this thesis. I made it!